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OBESITY AND DIABETES

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The frequency of the coexistence of obesity with diabetes is a matter of common knowledge. However obesity is not invariably associated with diabetes, nor are all diabetics obese. It is a matter of considerable interest to discover whether or not it is possible to relate the incidence of diabetes to one pattern of obesity and perhaps to explain why diabetes may develop in certain obese persons.

A brief discussion of some aspects of the metabolism of normal persons may be useful for purposes of orientation. It must be kept in mind that the living body is not static. At any given instant it represents the momentary residium of the stream of intake particles minus the stream of output particles. The magnitude of the daily exchange of mass and the energy content of that mass is impressive. The majority of adults burn between 2000 and 3000 calories per day depending upon body type and manner of life. The impact of this energy exchange upon the residual body is unknown because of the absence of information relative to the total energy content of the body. The exchange of mass is likewise large, ranging commonly from 4 to 8 pounds a day. Data have been published[4] which suggest that the average daily turnover of mass may be related to the size of the body. For normal persons the turnover approximates 5% of the body mass. In other words, a person turns over a mass of material which approximates his normal weight every 20 days.

What such a mass of exchange can mean to the evident body is illustrated by the following experiment. A 23-year-old girl with an average weight of 62.0 kilo was studied for 35 days (Duncan[1]). In this period she took in and put out an average of 3.17 kilos per day but in so doing she had an average daily weight change of only 300 gm. Thus with an average 5% daily mass exchange, she had only a 0.5% average daily body weight change. Such facts point up the tremendous rate of change of the material which goes to make up a body and yet the astounding average total stability of this body.

The present interest is in the carbohydrate fraction of this mass and energy stream. What is the ordinary turnover of carbohydrate? There are many published statements about the percentage of carbohydrate in normal diets. It may be noted that normal

bodies can function adequately over a wide range of carbohydrate intakes. In one series of 18 thin patients (Strang and Cox[5]), carbohydrate intake varied from 40 to 400 gm. per day without noteworthy physiologic stress. It seems probable that most of us use routinely between 200 and 400 gm. per day. In the picture of mass exchange, this level would approximate 5 to 10% of the daily mass exchange.

With a carbohydrate turnover of that mass and rate, it becomes important to identify at least the major features of the intake and of the output of carbohydrate. Most of the carbohydrate is taken into the body in more or less equal loads 2 or 3 times a day with intervals of 3 to 6 hours between loads. The digestion and absorption of these foods is extremely efficient and in most cases the process is essentially complete in 2 hours, varying of course with the nature of the meal. That means that, within 2 hours, 100 to 200 gm. of carbohydrate are taken into the body proper and disposed of. After a rest period of 2 to 4 hours, the load is repeated. Probably the body is subjected to this loading problem only 6 hours a day, but certainly at the peak periods great rates of change take place. Part of the carbohydrate is oxidized and part of it is stored.

An approximation of magnitude of the storage problem can be made if it is assumed that, during the postprandial period, the total energy needs of the body are supplied by carbohydrate combustion. In the basal state we normally burn 1 to 1¼ calories per minute. During moderate activity 2.5 calories per minute may be used. Since a gram of carbohydrate is equivalent to 4 calories, it is obvious that in the postprandial period, even with moderate associated activity, 0.5 to 0.75 gm. of carbohydrate per minute could suffice. The remainder of the carbohydrate load must therefore be stored. If we assume that the normal blood sugar is around 100 mg. per 100 ml. and if we assume that the normal circulating blood volume is about 5 L., it is apparent that roughly 5 gm. of glucose are in active circulation most of the time. The information provided by many glucose tolerance tests tells us that immediately after the ingestion of sugar, the blood sugar rises slightly but within a few moments is again normal. That means that, as a meal, or load of carbohydrate, is being absorbed, the rate of removal of carbohydrate from the blood must equal the rate of addition. In other words, the combined processes of oxidation and storage must be actively mobilized within a few moments. If a mixed carbohydrate meal containing 120 gm. is digested and absorbed in 2 hours, the average load is 1 gm. per minute for this period. If the sugar were not removed promptly the blood sugar would be 200 in 5 minutes, 300 in 10 minutes, and so on. However, normal persons have shown the ability to handle 2 to 3 gm. per minute for many minutes. If the body is burning 2.4 calories per minute (moderate activity), it could oxidize 0.6 gm. of carbohydrate per minute as a limit-value. If the rate of absorption is 1.0 gm. per minute, 0.4 gm. per minute must be stored; if absorption is 2.0 gm. per minute, 1.4 gm. must be stored. It will be noted that each increment in carbohydrate load falls entirely on the storage mechanisms. We must also note that this storage capacity must be maintained continuously throughout the absorption period of 1 to 2 hours, during which the body may pick up 100 to 200 gm. of carbohydrate. The magnitude of this carbohydrate storage burden should be recognized.

Carbohydrate is rapidly stored in the body as glycogen and as fat. The

glycogen cycle is familiar to all. It may be of value to restate a few of the basic facts about the storage of carbohydrate as fat (Duncan[1]). About 30% of the daily glucose supplements of a well nourished animal is converted into fat. Fat is formed directly in adipose tissue as well as in the liver. Probably glycogen is one stage in fat formation in the adipose tissue. Fat formation cannot proceed without insulin. It is a question whether the requirement of insulin for fat formation is not more important for the body than its requirement for carbohydrate oxidation. The fat molecule has over twice as much energy packed in it as does the carbohydrate molecule. Just how this energy is put into the molecule is not important here, but certainly oxygen is stripped off from carbon and hydrogen particles and the intermediary metabolism of carbohydrate produces this end result. Fat molecules once formed are not static. While fat is being actively stored, other fat molecules are being mobilized and burned. The carbohydrate storage mechanisms can and do handle easily loads of 2 to 4 gm. per minute for 1 to 3 hours at a time without evidence of strain. Ordinarily they rest between loads.

The second major feature of carbohydrate mass exchange is its oxidation. The details of the production of energy, CO_2 and water are not pertinent to the present discussion. It may be noted that energy transfer plays an important role in the storage problem. By and large, however, carbohydrate oxidation mechanisms have their greatest importance in output processes. In contrast to the intake problems, carbohydrate output, or oxidation, problems extend over the entire 24 hours a day. The rate of carbohydrate consumption varies greatly from hour to hour. Certain of the factors which influence this rate are of considerable importance to our present thesis. The dominant factor is the total metabolism of the body. Normally we burn 2000 to 3000 calories a day. This common form of expression can be restated as an average of 1.5 to 2.0 calories per minute. In the basal state 0.8 to 1.3 calories per minute may be used. Quoting from Passmore's[3] review, we note that washing, dressing and the like required 2.3 to 4.0 calories per minute; light work, 1.6 to 2.5; average work, 2.0 to 4.0; heavy work, 6.0 to 8.0 calories per minute. The point to note is that the energy requirements vary sharply from minute to minute, but in any event they must be met.

In general, the fuel for these energy needs comes from one or both of 2 fuel systems: the carbohydrate system and the fat system. It may be reemphasized that the energy needs of the body are going to be met, and if one system cannot supply them, the other must. Information as to the source of energy at any given instant is supplied by studies of the respiratory quotient. From such studies certain generalizations may arise. In most instances, fuel needs are supplied by both fuel systems. It is as if we had dual carburetors which operate cooperatively, each supplying its proportional share of the total. However, the ratio of carbohydrate fuel to fat fuel is not fixed. In general, the carbohydrate system is much more volatile. It responds quickly to sudden loads. The fat system adapts much less rapidly to sudden load change but seems to play a greater role in dealing with the general over-all level of metabolism. A second and equally important point is that the basic ratio between the 2 fuels can be changed by training. The body can adapt itself to a greater or a lesser carbohydrate or fat internal environment. How this is

brought about is not clear, but probably this type of training parallels other physiological training mechanisms, in that the body has intrinsically a certain rate of production of the necessary enzyme systems for the catalysis of the many intermediate steps in the energy extraction chains. By training, the rates of mobilization of these catalysts can be altered to meet repeated loading rates. Normal experience with the adaptation of races to extremes of diet supports this thesis. However, a simple illustration of this adaptation is provided by the training of patients for glucose tolerance tests whereby dormant carbohydrate handling capacities are mobilized to handle specific loads more efficiently. A comparable example is the adaptation of fat people to the higher rate of fat metabolism required by a reduction diet. The point for emphasis here is that the fuel jets in this carburetor are not rigidly fixed and that they vary in response to specific loads and also to training. The body can and does adapt to the fuel available to meet the required rate of metabolism.

"Carbohydrate Handling Capacity" is a useful term to indicate the over-all ability of the body to deal with the load of carbohydrate which is thrown upon it each day. Normal people can readily handle 300 to 500 gm. of carbohydrate a day without strain. What is the top limit of normal capacity? I do not know of any studies which have shown this top limit.

With regard to intake factors, the total carbohydrate handling capacity is considerably influenced by the type of carbohydrate employed and by the meal pattern. Complex sugars which require time for digestion and absorption reduce the peak of the gram-per-minute handling problem. Similarly it is common clinical experience that 300 gm. of carbohydrate divided into 6 feedings of 50 gm. taken at 4-hour intervals are more easily handled than 3 feedings of 100 gm. taken 4 hours apart. Proper periods of rest of the carbohydrate mechanisms likewise have a bearing, although overlong rest periods appear to reduce the efficiency of this operation.

A point of considerable importance is that the carbohydrate handling capacity is not a fixed property of the body any more than are body temperature, oxygen consumption or even blood pressure. Factors known to influence carbohydrate handling capacity are training, infection, trauma, muscular activity and overloading. A person can be trained by dietary discipline to handle greater or lesser amounts of carbohydrate as is shown by training for glucose tolerance tests. Infection and trauma sharply reduce carbohydrate-handling capacity. Muscular activity increases carbohydrate-handling capacity. Prolonged excessive overloading of the carbohydrate handling capacity results in decrease of capacity or "strain," just as excessive overloading strains a muscle or other functioning area of the body.

In a similar manner, the over-all capacity of the body to deal with the mass of fat exchange each day can be described as its fat-handling capacity. As with the carbohydrate load, the main problems in fat handling are those of dealing with the intake load and with the oxidation load. The maximum figure for the amount of fat which can be turned over each day is not known. Some information as to fat intake can be obtained from studies made on patients who were gaining weight (Strang and Cox[5]). Diets with fat contents of 130 to 330 gm. per day, which corresponded to from 55 to 90% of the caloric contents of the diets, were handled efficiently and without strain. As these

loads were divided into 3 meals, it is evident that even small people can deal with single fat loads of 50 to 120 gm. The digestion and absorption may take 3 to 4 hours, in contrast to the shorter time for carbohydrates. Data on the changes which occur in the blood and the mechanisms of the removal of fat from the blood are not as clearly defined as in the case of carbohydrate. Certainly they do operate with efficiency, as the reported changes in blood lipoids postprandially are definitely limited. Ingested fat may be stored directly in the liver and also in the adipose tissue. Many studies have shown the deposition of food fats in body fat stores under conditions of forced fat feedings, thereby indicating one mechanism of the rapid blood clearance.

The rate of oxidation of fat in normal persons varies greatly. It would appear that the body preferentially burns carbohydrate when it is available, but in its absence, fat burns readily. If the respiratory quotient is used as an index of the fuel being used, our studies (Strang, McClugage and Brownlee[8]) on thin people show one patient whose fasting respiratory quotient varied from 0.92 to 1.0 over a period of 6 weeks during which he took in 326 gm. of fat per day but at the same time took in 400 gm. of carbohydrate. In contrast, another patient had fasting respiratory quotients varying from 0.71 to 0.75 over a period of 3 weeks, in which she took in 333 gm. of fat per day but only 41 gm. of carbohydrate. Such observations indicate not only the preference for carbohydrate fuel but also the great range of adaptability to the available fuel supply. From the point of view of the maximum rate for the efficient oxidation of fat, we note the frequently quoted value of 2.5 gm. of fat per kilo of body weight as the limiting rate. Other evidence indicates the importance in the problem of the total amount of fat oxidized of the direct oxidation of fat by muscle cells.

In general, we may consider that the body has a certain fat-handling capacity for dealing with the mass of fat which is turned over each day. This complex property of the body is not fixed but varies with the body needs. Training influences the efficient handling of intake loads. Training as well as availability affects the facility with which oxidation loads are met. The evidence is not so clear that illness and trauma reduce fat-handling capacity as is the case with carbohydrate handling. However, it is probable that relative inactivity of fat-handling mechanisms can reduce the over-all capacity at any given time. The important point is that the body can and does adapt itself to great variations in the fat component of its internal environment.

In summary, it may be noted that the normal body is in a state of rapid flux. The carbohydrate component of this daily turnover of mass and energy is quite variable. The capacity of the body for handling the loads of carbohydrate has certain natural variations. Fat also is an important component of the daily mass and energy turnover. Again the over-all fat-handling capacity is not a fixed property. There is an interrelationship between the carbohydrate-handling capacity and the fat-handling capacity, the governing principle of which is the need of the body for fuel. This demand for energy must be met. The source of energy at any given moment will depend not only upon the supplies available to the 2 main fuel systems as reflected in the carbohydrate-handling capacity and the fat-handling capacity, but also upon the adaptation of the body to each of these fuel systems.

FACTS ABOUT OBESE PERSONS. Obese

persons show certain fairly characteristic deviations from the patterns of metabolism which have just been described for persons of normal weight.

The mass exchange and the energy content of that mass exchange are considerably increased in the obese, the increase in both being somewhat related to the excess of weight. For example, one group of 3 patients[4], who averaged 81% overweight, had an average intake of 4400 gm. per day and a urine output of 2600 gm. per day. These values are about 50% greater than normal. The calculated insensible weight loss was likewise over 50% greater than normal. It would appear, then, that the mass overturn each day, although it is somewhat less than 5% postulated for normals, is quite large. Many studies of the energy exchange likewise show large increases over normal levels. In one series of 7 patients who were overweight an average of 83% (Strang and Evans[6]), the basal metabolism alone averaged 26% above the calculated normal for these persons. This increment was 15 calories per hour in absolute units or 360 calories per day. Such an elevation in basal metabolism alone corresponds to about 15% of the total metabolism of active persons of normal weight. Thus in the obese we have the dynamic picture of large quantities of mass and energy constantly turning over in a body of much larger residual mass.

Associated with these high rates of mass and energy exchange is a much larger mass of carbohydrate exchange. Even when the distribution of ingested foods into protein, fat and carbohydrate follows a fairly normal pattern, an intake of 350 to 500 gm. of carbohydrate per day is not unusual. Again, it should be noted that this intake load is usually spread over less than one-third of the 24-hour period.

In the experience of many observers, obese persons fall into 2 main groups, the "plethoric" and the "anemic," which have fairly characteristic food intake patterns. The plethoric type, the "gross feeder" is a big man who eats large quantities of all kinds of foods, protein, fat and carbohydrate. The proportions of intake are distributed among the 3 food groups much as for normal persons. It is obvious that fats and concentrated carbohydrates must both be high in absolute amounts in order to obtain intakes of 3500 to 4000 calories per day. These people take in 350 to 500 gm. of carbohydrate daily but also large amounts of protein and fat. The "anemic" type is the fat woman over 40 who for years has taken in a diet low in protein, somewhat higher in fat but truly high in carbohydrate. In this case the 350 to 500 gm. of carbohydrate are out of proportion to the protein and fat. It is of special significance that this person takes one or perhaps 2 meals a day but frequently gets much of her intake from the almost incessant nibbling of concentrated carbohydrate snacks. The patients whom we see in practice are blends of the 2 types described, but it is noteworthy how frequently one dominant type is in evidence.

The maximum carbohydrate-handling capacity of obese persons has never been determined any more than for normal persons. However, with the increase in carbohydrate food loads which we have just mentioned, the ability of the body to oxidize part, and to store the rest, of the intake is adequate for the load in the vast majority of obese persons. Ogilvie[2] reported observations which show that in early obesity, the body can handle carbohydrate loads more efficiently than normal. This is in agreement with our previous observations that carbohydrate-handing capacity can improve with training. Certainly these people

deal with minute loads of 3 to 4 gm. as well as normal persons handle their 1 to 2 gm. per minute load. However, we do not know the maximum capacity for the intake of normal persons. Whether the ceiling for carbohydrate handling is any higher in the obese is likewise not known.

The total metabolism is higher in the obese, which means that the demand for fuel each minute may be 10 to 50% greater than normal. Here again we find that ordinarily the obese obtain energy from the carbohydrate-combustion cycle and the fat-combustion cycle. If our interpretation of respiratory quotient studies is correct, the obese get rather more of their basic energy needs from fat metabolism for, in general, the respiratory quotient in the fasting state tends to be lower than for persons of normal weight (Strang and McClugage[7]). To be sure the carbohydrate system is functioning well and quickly adapts to sudden loads. However, if we resort again to our carburetor phraseology, we could say that fat-energy jet is set at a wider opening. Of any 100 calories required by the body, more of them are supplied from fat oxidation than from carbohydrate oxidation. This would be true especially in the 16 to 20 hours a day when the effect of the carbohydrate intake loads no longer dominate the fuel available for energy. The rapid and efficient removal of postprandial circulating carbohydrate, especially by fat formation, coupled with the elevated metabolism also tends to minimize in the ordinary obese patient the prolonged utilization of carbohydrate for energy such as was noted above in the thin man who took in 400 gm. of carbohydrate per day (Strang, McClugage and Brownlee[8]). Respiratory quotient studies on obese patients after standard test meals indicate that with the same carbohydrate load, the obese, even in the presence of adequate carbohydrate, fail to show the same degree of elevation of respiratory quotient which is found in persons of normal weight (Strang and McClugage[7]). It would appear from this and other related studies that, although large amounts of carbohydrate are introduced into the obese body, they are quickly stored, much of it as fat. The body tends to adapt itself to an internal environment in which a greater proportion of the increased total metabolism is supplied by fat, although the absolute amount of carbohydrate burned may not be much different from the normal mass.

Evidence is likewise available that the efficiency of the fat oxidation system also is greater in the obese. In normal persons 2.5 gm. fat per kilo per day represents approximately the ordinary limit of efficient fat handling. Many obese persons can burn 3 to 3.5 gm. per kilo per day without evidence of strain (Duncan[1]). Here again we have evidence of the ability of the organism to adapt itself to its internal environment and, by training, to improve a functional capacity, in this instance fat-handling capacity.

In obesity, therefore, we have the picture of the efficient operation of a high capacity system for the turnover of mass and energy. By training, the carbohydrate-handling capacity and the fat-handling capacity of the body improve sufficiently so that the body can adapt itself to meet the demands.

DIABETES. The definition of diabetes which is offered here is based on the concept of a human body outlined above, a body which represents the transient equilibrium between a stream of intake and a stream of output of mass and its energy content. Diabetes is a physiological imbalance in which the carbohydrate-handling capacity of the body cannot meet the carbohy-

drate load which is being thrown upon it at a given time. This definition includes both of the main phases of carbohydrate metabolism, storage and oxidation. It does not depend upon the identification of any single defect. It recognizes that the defect may be in different areas in different types of patients. The degree of defect, in absolute units, is not of too great moment. The one property common to all diabetics is that the body cannot handle the load of carbohydrate metabolism which is thrown upon it at a given time.

The criteria of a strained carbohydrate-handling capacity warrant brief discussion. The result of the failure of the storage mechanisms to remove sugar from the blood as fast as it is poured into it from the gut is readily appreciated. The blood sugar rises promptly to a level at which mass action can produce a balance between rate of storage and rate of intake. Glycosuria is quite characteristic of this phase. The prolonged elevation of blood sugar has been considered as an adaptive mechanism for forcing carbohydrate metabolism in the face of relatively defective catalysts in accord with the mass laws of chemistry. The body readjusts its normal concentrations of blood sugar to meet a metabolic demand. The later readjustment of the kidney, the so-called high threshhold, may represent an additional reorientation, so that the driving force of the high blood sugar can be maintained without the handicap of the wastage of sugar in the urine. None of these or comparable laboratory criteria is absolute. Only when the preponderance of laboratory evidence, particularly that obtained by a standard loading test, indicates a less than average carbohydrate-handling capacity is a diagnosis of diabetes entertained. When clinical evidence of imbalance is also available, the diagnosis is more certain.

If this general concept of diabetes is correct all persons are potentially diabetic in that theoretically it is possible to overstep the carbohydrate-handling capacity of anyone. In practice only those persons with relatively low total carbohydrate-handling capacity are in jeopardy. When factors which normally tend to reduce carbohydrate-handling capacity coincide with conditions which abruptly increase carbohydrate load, strain results. Dramatic confirmation of this is commonly provided by infections. Here the abrupt loss of carbohydrate-handling capacity coincides with the increased metabolic load and frequently with an abrupt shift to the customary high carbohydrate invalid diet. Thus both the supply of carbohydrate and the need for carbohydrate metabolism are increased at a time when the body's ability to deal with carbohydrate is reduced.

We are also interested in the possibility of dietary indiscretion alone as a mechanism of strain production. Acute diabetes resulting from acute gross overloading of an apparently normal person is not common, and even less common is apparent complete recovery. Such a man was observed a few years ago. This man, of normal weight but indolent habits, went to Florida for a vacation. He liked the fresh orange juice and drank 1 to 2 quarts a day. Symptoms developed before his return home 2 to 3 weeks later. After regulation he was discharged from the hospital on a maintenance program which contained 250 gm. carbohydrate and required 60 units of insulin. Over the next 2 years his insulin needs dropped to 25 for the same diet. In the course of the following 2 years he was taken off insulin. He was observed for 2 additional years during which he

maintained normal signs while still following the same diet and manner of life. This man is an example of an acute sprain of the carbohydrate handling capacity due to carbohydrate overloading. It is significant that he largely recovered in time.

The chronic diabetic state is relatively common. In this condition the carbohydrate-handling capacity is consistently lower than average. Even in his best periods the patient has an innate capacity close to or below his requirements. The locus of failure in the majority of diabetics is in the storage areas. Their chief troubles come after meals when the storage load is added abruptly to the oxidation load. In most of these patients reduction of the storage load alone suffices to restore a positive carbohydrate-handling capacity balance. In severer grades of diabetes the carbohydrate oxidation chain is also seriously disturbed. The total carbohydrate-handling capacity which remains after impairment in both storage and oxidation areas is so low that the minimum needs of the body for carbohydrate metabolism can scarcely be met. The diabetes is an imbalance between carbohydrate-handling capacity and body needs for carbohydrate metabolism, both of which physiologic complexes are capable of considerable independent variation.

Earlier it was mentioned that the carbohydrate-handling capacity is not a fixed property of any body. It is normally diminished by inactivity of even 10 to 12 hours' duration. Body trauma, especially trauma of the central nervous system, may reduce it. Infection drops it sharply. It may be reduced by prolonged overtaxing of its normal limits. It can be improved by recovery from trauma or infection. It can be improved by training. Diabetes likewise is never absolute, there is always some carbohydrate oxidation and some carbohydrate storage. Whether or not the capacity approximates the need for oxidation or for storage at a given time is the significant feature. Thus, like carbohydrate-handling capacity, diabetes is not a fixed property of any body. If it is possible by any means to reduce the carbohydrate load below the capacity of the body to handle it, the physiologic imbalance is rectified and the patient is no longer physiologically diabetic.

There are many systems for the treatment of diabetes. Where moderate carbohydrate diets are combined with sufficient insulin to produce normal blood sugars and negative urines, emphasis is being placed upon a large carbohydrate turnover and large carbohydrate component of the total metabolism controlled by meticulous attention to the form and distribution of carbohydrate intake load and to the distribution of insulin to care for storage and oxidation loads. The "free diet" advocates appear to be little concerned with the mass of carbohydrate turnover, provided that enough insulin is present to care for some carbohydrate storage and sufficient carbohydrate oxidation so that the load on the fat metabolism is not too great. In earlier days a great point of treatment was the reduction of the absolute mass of carbohydrate, thus sparing the storage function and shifting the great bulk of the metabolic load to the fat-handling system. That successful symptom control is possible by all of these methods and their many modifications suggests that the most important feature in diabetes is the need of the body to meet its fuel requirements. Since alternate pathways are available for energy supply, success may be obtained by bolstering the carbohydrate fuel system, by retraining the fat fuel system to take a greater share

of the total load, or by any combination of the two.

DIABETES AND OBESITY. The preceding description of a point of view regarding normal carbohydrate-handling capacity, obesity and diabetes leads to the discussion of the relation of obesity to diabetes. The abnormal frequency of the coexistence of obesity and diabetes has been well established. It is interesting to note, however, that all obese persons are not diabetic and that all diabetics are not or have not been obese. Diabetes is seen most frequently in a certain type of obese patient. The patients are usually over 40; they are more commonly female; they tend to be of a passive indolent nature; they have been obese for a long time.

In the discussion of obesity, the so-called "anemic" type of obesity was described. The similarity between the type of obese patient who has diabetes and the "anemic type" obesity is so striking that we may wonder whether or not these two conditions are causally related, that is, the obesity causes the diabetes or *vice versa*, or whether the two clinical conditions are the result of some cause common to both of these states.

The characteristic diet of these obese patients is high in carbohydrate and low in protein. From the above discussion of carbohydrate-handling capacity it may be noted that this capacity can be improved for a time by training with increased carbohydrate feeding. Ogilvie[2] reported the improved glucose tolerance in the early years of obesity. However, as the carbohydrate load increases, the tolerance approaches the upper limit of the natural carbohydrate-handling capacity. In this connection it is also well to notice that this type of feeder is not only a high carbohydrate feeder but frequently a nibbler. She may eat only 1 or 2 large meals a day. However, much of the day she is taking repeated doses of carbohydrate. The point to be made here is that these patients never give their carbohydrate-storing or carbohydrate-oxidizing mechanisms a chance to rest. What this can mean to the person who begins to have a prolongation in the glucose tolerance curve, as seen in the earliest phases of diabetes, can well be appreciated. In all probability, prolonged excessive intake alone can seriously impair carbohydrate-handling capacity of the body.

The level of total metabolism increases with the development of obesity. The need for carbohydrate metabolism increases in this type of obese patient. In the discussion of normal metabolism it was stressed that the body is going to get its energy needs; that these energy needs came mainly from a carbohydrate system and a fat system; that the body can readily adjust itself to either fuel type, rapidly in the case of carbohydrate, more slowly in the case of fat. In considering the metabolism in obesity we noted that the total level of metabolism is increased; that the adaptation to carbohydrate demand is present in simple obesity; that nevertheless the proportion of total energy need supplied by fat is greater: certainly in the basal state and likewise 3 to 4 hours postprandially. If we may use our carburetor illustration again, we would say that in the simple obese the fat jet is somewhat more widely opened than the carbohydrate jet which may, however, be normal in size. Now, what happens in patients who nibble carbohydrate many hours a day and who become inactive as well as obese? The abundant carbohydrate supply tends to shift the body to almost complete carbohydrate fuel for most of the day. The body becomes adapted to a high carbohydrate, lower fat mixture. The

carbohydrate jet opens wider, the fat jet gets smaller from disuse. In other words, in the development of obesity of this type, the larger body not only requires a greater level of total metabolism but also demands a higher proportion of this increased level from carbohydrate.

As time goes on, the margin of safety between carbohydrate-handling capacity and the load becomes narrower. It is in this period that the natural factors which tend to reduce carbohydrate-handling capacity, such as trauma, infection, and others, can cause a sharp drop in the carbohydrate-handling capacity well below the body requirements and a strain ensues. The severity of the strain will vary from mild to severe, and we can well picture that the border of capacity is crossed in both directions (strain and recovery) many times before a significant and fairly chronic state of imbalance finally develops. When a strain of carbohydrate-handling capacity now occurs, we not only have an overtaxing of the storage and oxidation facilities for carbohydrate but we have in addition a machine which has become adapted to a high rate of carbohydrate fuel to meet its requirements. With the failure of the carbohydrate system, the fat system is required to adjust abruptly to meet the total load. Since the fat system is not accustomed to meet sudden demands, we often see evidences of strain and then decompensation of the fat-handling system. Ketonemia increases, then ketonuria, then the full picture of acidosis. This concept of the obese diabetic starts with a long term high-carbohydrate, low-protein diet which produces a poorly muscled individual who has a high total level of metabolism which is being supplied largely by the carbohydrate fuel system. As the obesity increases, so does the total metabolic load and the load on the carbohydrate handling capacity while the fat handling system hibernates. Persistent overstepping of the carbohydrate-handling capacity results in diabetes which for long periods is manifest chiefly in the poor storage of carbohydrate. With an illness, or other cause of the abrupt loss of carbohydrate-handling capacity, the full impact of the total metabolic load falls on the untrained fat fuel system which in its turn may fail to meet the body demands.

Thus diabetes and obesity are related in many people. The link is through the diet which not only caused the obesity in these persons but also strained the carbohydrate-handling capacity over the long period of weight gaining and set the stage for the development of diabetes.

The treatment of the type of diabetes associated with obesity centers around the reduction of the obesity. There are many reports of the disappearance of the diabetic state following the removal of even modest quantities of fat. Apparently any adequate reduction program provides satisfactory results, certainly in the milder forms of diabetes. If our thesis is correct, the mechanism of this form of therapy is both in the increase of the carbohydrate-handling capacity of the body and in the lowering of the total requirements for carbohydrate metabolism so that an equilibrium between capacity and demand is re-established. The carbohydrate-handling capacity can be improved by any and all of the devices mentioned above. The removal of infection and trauma are obvious. Sharp reduction in the carbohydrate load below the limits of capacity permits the gradual retraining of this function. In the obese patient with mild diabetes a reduction of the carbohydrate intake load and the natural proc-

esses of retraining of the carbohydrate-handling capacity suffice. More severe decompensations require aid to supply the carbohydrate handling capacity essential for the needs of the body. Insulin is the prop supplied, and, by its help in both storage and oxidation processes, insulin brings the carbohydrate-handling capacity up to the levels required for body needs. However it should be recalled that insulin, by its influence on fat formation, as well as on glycogen formation and oxidation, tends to discourage the natural increase in the fat fuel component of the total metabolism.

The lowering of the body requirements for carbohydrate handling can be promoted in 3 ways: 1) Reduce the level of carbohydrate mass exchange; 2) reduce the total metabolic load; and 3) reduce the proportion of the total metabolic load which is provided by carbohydrate.

The reduction of the level of carbohydrate intake load is one of the oldest methods of treatment of diabetes. There is, however, a minimum limit beyond which carbohydrate reduction cannot be carried. The usual diets for weight reduction are low-carbohydrate diets.

The reduction of the total metabolic load is important. The immediate effects of arrested infections and restricted activities, even to bed rest for a time, are obvious. The benefits of the reduction of the metabolic load due to the obesity are obtained only by prolonged painstaking dieting. A 20 to 40% reduction in metabolic load can readily be obtained from the combined benefits of lowered basal metabolism and improved body efficiency following weight reduction.

The reduction of the proportion of the metabolic load provided by carbohydrate is an additional important adaptation. It was pointed out that in this particular type of patient with diabetes and obesity the body has become adapted to a high carbohydrate-low fat fuel mixture. It must be kept in mind that the body is going to get its energy needs somehow. If, therefore, we can retrain the fat fuel system to increase its capacity and take over a larger share of the total metabolic load, a corresponding benefit accrues by the removal of a significant load from an already struggling carbohydrate-handling capacity. The system of high-fat diets for diabetes of all varieties, which was used extensively by Newburgh many years ago, took advantage of this principle. Prolonged adherence to a reduction diet promotes this adaptation.

Muscular activity has a very beneficial influence on the carbohydrate-handling capacity and definitely tends to improve it. In short spurts, a betterment in carbohydrate oxidation mechanisms undoubtedly occurs. In long range training programs it is probable that an increase in the facility with which muscles can extract energy from fat affords additional benefit by taking a greater proportionate share of the metabolic load and thus reducing the carbohydrate requirement. It is possible that effect of the poor muscular development which results from the prolonged low protein diet of the obese patients of this type adds its special load at this point. Only when these patients have reduced sufficiently to permit real muscle training can this additional aid to fat handling be secured.

Standard reduction diets tend to retrain the fat fuel system. Under these dietary conditions the fuel mixture which is metabolized may have 80 or even 90% fat. It is in this field of the retraining of the fat fuel system that

Orinase may play its role. Orinase, by slowing down the facility with which the liver gives up its glycogen, tends to keep blood sugar levels down but without increasing carbohydrate oxidation and thereby forces the utilization of fat fuel. Those patients who have relatively well developed fat fuel systems, although they may have been dormant as with this type of obese person, can be given that extra urge by Orinase to develop the fat-handling mechanisms. Those patients who have inadequate fat fuel systems or who have strained them as well as the carbohydrate-handling capacities, as is the case with most thin diabetic patients, cannot be helped by Orinase. When insulin is employed to insure proper metabolism of even moderate carbohydrate intakes, the body demand for fat metabolism is diminished and thus the natural stimulus to improve fat utilization is reduced. As a consequence, the benefits to a patient from the use of Orinase are minimized by the previous or concurrent use of insulin. Most of the established clinical facts about the action of Orinase in its relation to carbohydrate and fat metabolism are consistent with this hypothesis.

Summary. A concept of the problem of the obese diabetic has been developed. The normal person with his tremendous rate of exchange of mass and energy is described. The carbohydrate handling capacity, its components and particularly its physiologic variations are discussed. It has been emphasized that the metabolic load of the body must be met and that a carbohydrate fuel system and a fat fuel system normally cooperate to do this.

Obesity adds certain special features to this exchange picture. Especially noteworthy are the increased rates of both mass and energy exchange and the potential adaptions to carbohydrate and to fat fuel in certain forms of obesity.

Diabetes complicates the situation further in that the carbohydrate-handling capacity becomes diminished below body needs. Diet excesses alone can cause strain of the carbohydrate-handling capacity.

In the obese who become diabetic, the failure of the carbohydrate-handling capacity has resulted from prolonged overtaxing of the carbohydrate-handling capacity associated with the long time use of high carbohydrate, low protein diets. This state develops at a time when the total metabolic load has been raised due to the obesity and, in addition, at a time when the body has become adapted to a carbohydrate fuel system, also as a result of the prolonged high carbohydrate intake.

The treatment of these obese diabetic patients obviously is to reduce the strain on the carbohydrate-handling capacity by reducing the carbohydrate exchange below the ability of the body to deal with it or by improving the ability of the body to handle the excessive carbohydrate load by the use of insulin. A reduction in the total metabolic load likewise reduces the strain on the carbohydrate-handling capacity. Furthermore, a readaptation of the body to obtain a higher proportion of its energy from the fat fuel system reduces the load on the carbohydrate-handling capacity. In our opinion, Orinase facilitates this readaptation. The end result of successful therapy is a body of normal proportions and normal mass and energy exchange which has a carbohydrate-handling capacity well above the immediate bodily requirements. The vast majority of obese diabetic patients can attain this end by prolonged adherence to a proper reduction regimen.

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SUMMARIO IN INTERLINGUA

Obesitate E Diabete

Es disveloppate un concepto del problema del diabetico obese. Es describite le subjecto normal con su tremende excambio de massa e de energia. Le capacitate de manear hydrato de carbon es discutite, etiam su componentes e particularmente su variationes physiologic. Es sublineate le facto que le requirimentos metabolic del corpore debe esser satisfacite e que normalmente un systema a combustion de hydrato de carbon e un systema a combustion de grassia collabora in effectuar iste objectivo.

Le presentia de obesitate adde certe aspectos special a iste situation de excambio. Es specialmente notabile le accelerate excambio de massa e de energia e, in certe formas de obesitate, le adaptation potential al combustion de hydrato de carbon e de grassia.

Diabete rende le situation ancora plus complicate in tanto que le capacitate de manear hydrato de carbon es reducite a infra le nivello del requirimentos corporee. Excessos de dieta per se es frequentemente un supercarga pro le capacitate de manear hyratos de carbon.

In individuos obese qui deveni diabetic, le collapso del capacitate de manear hydrato de carbon es le resultato de un prolongate supercarga del capacitate de manear hydrato de carbon in association con longe periodos de dietas ric in hydrato de carbon e povre in proteina. Iste situation se disveloppa a un tempore quando le total carga metabolic es augmentate in consequentia del obesitate e, in plus, a un tempore quando le corpore se ha adaptate al systema de comburer hydrato de carbon, etiam in consequentia del prolongate ingestion de alte quantitates de hydrato de carbon.

Le tractamento de iste diabeticos obese require obviemente reducer le carga del capacitate de manear hydrato de carbon per reducer le excambio de hydrato de carbon a infra le limites del capacitate del corpore de manear lo o per meliorar le capacitate del corpore de manear le carga excessive de hydrato de carbon per medio del uso de insulina. Un reduction del total carga metabolic effectua equalmente un reduction del carga pro le capacitate de manear hydrato de carbon. In plus, un re-adaptation del corpore a obtener un plus alte proportion de su energia ab le systema del combustion de grassia reduce le carga pro le capacitate de manear hydrato de carbon. In nostre opinion, Orinase es de adjuta in effectuar ille re-adaptation. Le resultato final de un therapia successose es un corpore de proportiones normal e de normal excambio de massa e energia que possede un capacitate de manear hydrato de carbon liberalmente supra le requirimentos immediate del corpore. Le vaste majoritate del diabeticos obese pote attinger iste objectivo per sequer prolongatemente un appropriate regime de reduction de peso.

OBSERVATIONS ON THE EXCRETION OF TYPE 1 POLIOVIRUS FROM CASES AND THEIR CONTACTS

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Several workers have expressed views on the application of quarantine measures for the prevention of poliomyelitis. Many of these views have been based on epidemiological findings which are summarized in the recommendations of the expert committee of the World Health Organization (1954) that "Children with familial or intimate exposure should be confined to their homes for 21 days. Adults need not be confined . . . they should refrain from association with children other than their own and should avoid intimate contact with adults[8]."

Other workers have reported findings which are at variance with this recommendation. Melnick and Ledinko[3] (1953) showed that during a summer epidemic of Type 1 poliomyelitis, the ratio of subclinical infections to clinical cases was as high as 175 to 1 in children aged less than 1 year and somewhat lower in older children. Goffe and Parfitt[1] (1955) and Miller and Kamitsuka[4] (1956) have, with others, offered further evidence to support the suggestion that the virus is much more widely disseminated than is suggested by the number of clinical cases.

This laboratory has attempted isolation of poliovirus since July, 1956, from feces, and in certain instances throat swabs, obtained from patients and healthy contacts. This material has been tested in HeLa cells by a method resembling those described by Mitchell and Tomlinson[7] (1956) and Macrae and Stokes[6] (1957). Since June, 1957, the period of limited contact of the fecal extract with the cell layer has been abandoned and 0.1 ml. of this extract has been inoculated directly into maintenance medium in the tube and the tube observed for 6 to 7 days or until degeneration has occurred. Whenever virus has been isolated from feces, its identity has been established by neutralization tests using monospecific hyperimmune monkey sera prepared from each of the three types of poliovirus.

Specimens were received from most of the patients with poliomyelitis in this area. In many instances it was possible to examine repeated specimens of feces, collected at approximately weekly intervals, from individual patients and from home contacts of these patients.

From July, 1956, until the end of 1957, Type 1 poliovirus was isolated from two or more specimens of feces from each of 93 patients who were considered clinically to have nonparalytic or paralytic poliomyelitis. In 69 of these, records of positive stools followed by a final negative stool were available. Figure 1 shows as the ordi-

nate, the logarithms of the accumulated percentages of 93 patients from whose stools Type 1 poliovirus was isolated, and, as the abscissa, the weeks after onset of the illness in which the

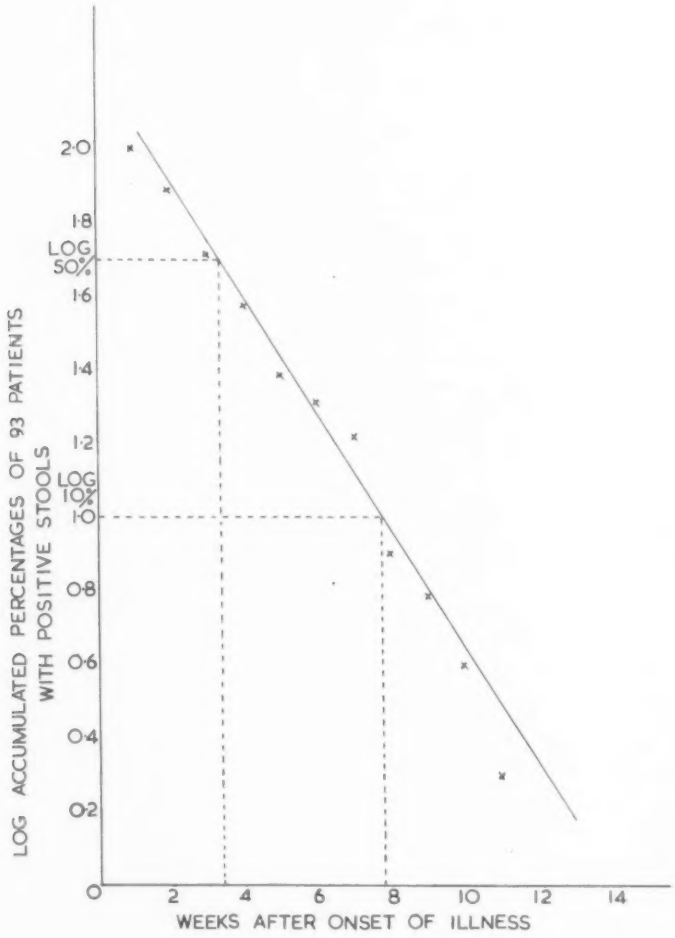

Fig. 1

specimen was taken. Figure 2 shows the logarithms of the weekly accumulated percentages of 69 patients from whom Type 1 poliovirus was isolated and the weekly accumulated percentages of final negative stools from the same group. Figures 3 and 4 show similar figures to those in Figs. 1 and 2 but are the records of 97 and 80 healthy contacts respectively, where the period of excretion has been calculated from the date of onset of the illness of the patients with whom they were in contact.

During this analysis it was observed that poliovirus was not always found in the samples taken during the period of excretion. In 28 of 149 patients and contacts to whom Figs. 2 and 4 refer,

from whom poliovirus had been obtained, negative results were followed by positive stools. A further 28 of the same group had at least three consecutive negative stools after the last isolation of virus; 8 of this group had had

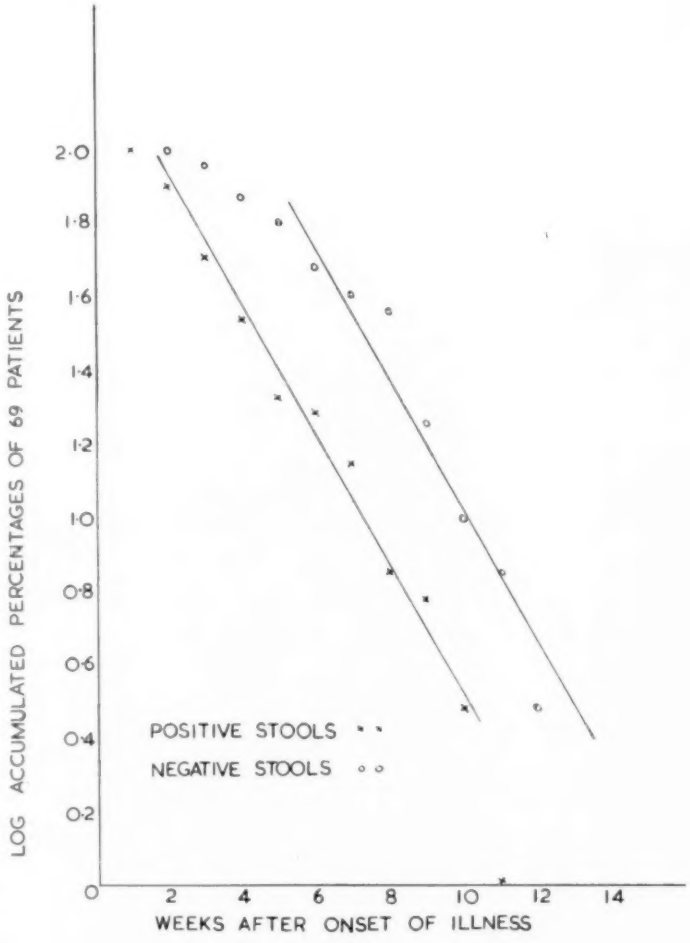

Fig. 2

negative stools interspersed between positive stools before three consecutive stools were found to be negative.

Discussion. From the graphs it appears that half the number of patients with poliomyelitis would be expected to excrete virus for about 3 weeks after the onset of their illness and that only after 8 weeks will this proportion fall to less than 10%. Half the healthy contacts can be expected to excrete virus for about 5 weeks after the onset of illness in the index case, and the proportion will not fall below 10% until 8 to 10 weeks have elapsed. These findings suggest that the rate of clearance of poliovirus from the stools follows an exponential curve. They closely re-

semble those of Kwantes[2] (1952) and other writers who found that the clearance rate of *Salmonella typhimurium* from stools during an outbreak was exponential giving 50% clearance at about 3 weeks.

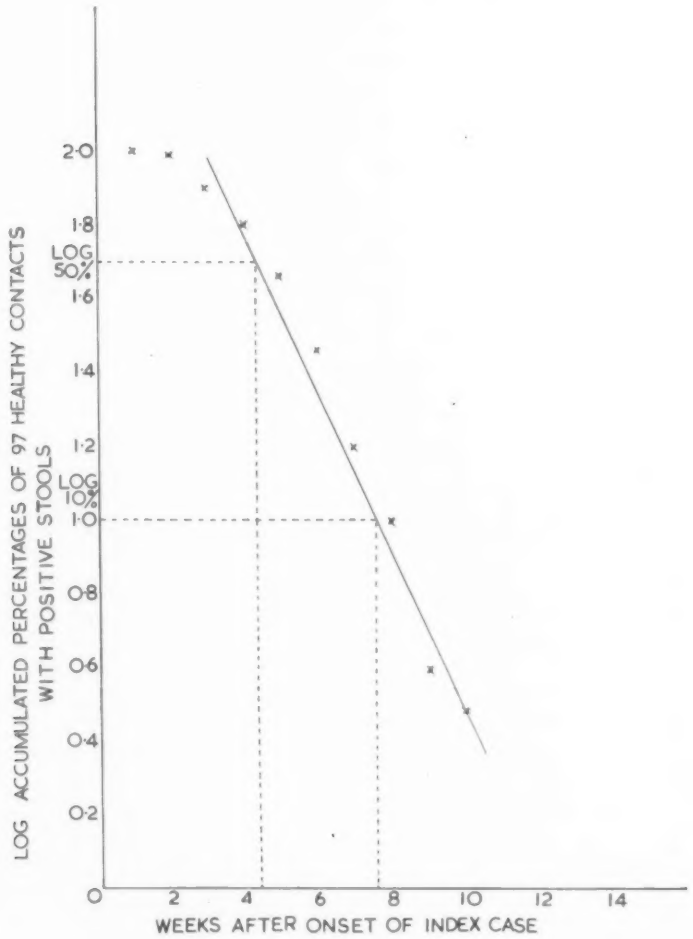

Fig. 3

On Figs. 2 and 4 there is a lag of weeks between the times at which the last positive stools were obtained and the times when the first presumed negative stools were obtained. This lag can be accounted for by an irregularity in the sampling time, due partly to the fact that most of the cases and healthy contacts were excreting during the peak holiday months of the late summer, and partly to the difficulty in obtaining specimens from patients in the first few weeks after their discharge from hospital when often they were convalescing away from their home.

Since, in 28 of 149 persons negative results were followed by further posi-

tive stools, it seems reasonable to suppose that these figures underestimate rather than overestimate the period of excretion. HeLa cells are generally regarded as being slightly less sensitive than other tissue cells in the detection of poliovirus in feces, and it may well be that these figures understate the length of the period of excretion of poliovirus. This small series, however, indicates that the potential dangers arising out of the presence of poliovirus in the stools of a large proportion of convalescent patients and home contacts may persist longer than is generally recognized, though, in the absence of information on the amount of virus excreted, it would be unjustifiable to assume that the danger remains the same throughout the period of excretion. A Public Health Laboratory Service Report[5] (1957), has pointed out that the 3-week period of quarantine is arbitrary,

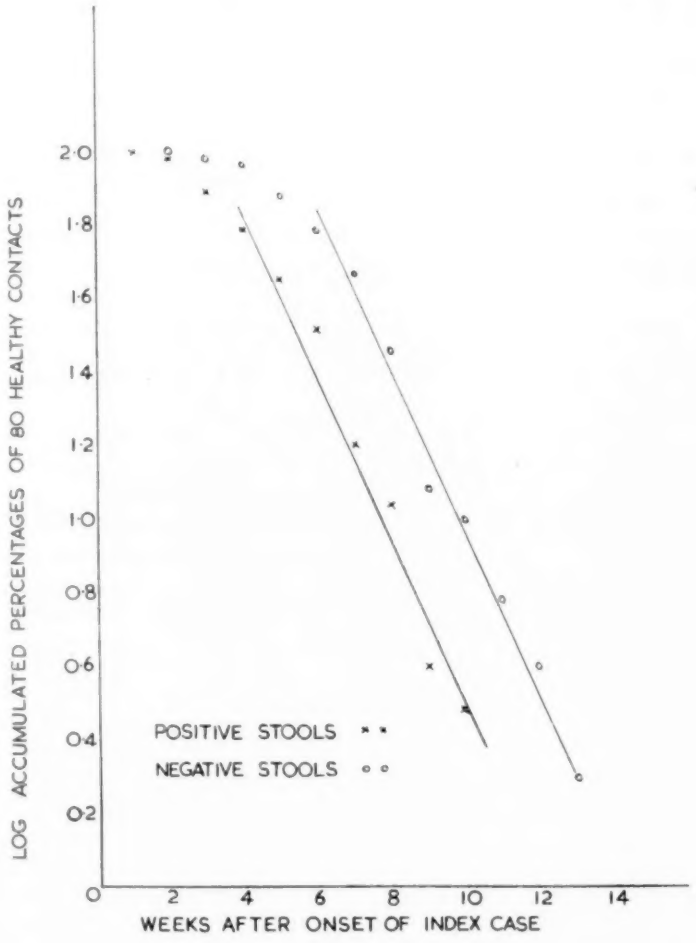

Fig. 4

it is limited by the difficulties of enforcement, and there is little likelihood that the contacts are much less infectious at the end than at the beginning. It is suggested that since the period of excretion exceeds 3 weeks in about half of the cases and about three-quarters of the contacts examined here, the value of the present quarantine period is limited. It is not intended, however, that this finding should be used in support of extending the period of quarantine. These figures also suggest that the examination of repeated specimens of stools from suspected cases or contacts may yield valuable information even when taken 3 to 6 weeks after the onset of illness.

Summary. From July, 1956, until the end of 1957, Type 1 poliovirus was isolated from two or more specimens of feces from each of 93 patients with clinical poliomyelitis and from each of 97 healthy contacts. Examination of the records of these specimens suggests that the clearance rate of poliovirus from stools of such excreters follows an exponential curve. The 50% clearance time for patients is about 3 weeks after the onset of the illness, and that for healthy contacts is about 5 weeks after the date of onset of symptoms in the index case.

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SUMMARIO IN INTERLINGUA

Observationes In Re Le Excretion De Virus De Poliomyelitis Typo 1 Per Patientes E Per Subjectos Qui Se Trova In Contacto Con Tales

Inter julio 1956 e le fin de 1957, virus de poliomyelitis Typo 1 esseva isolate ab duo o plus specimens de fece in cata un de 93 patientes de poliomyelitis clinic e in cata un de 97 subjectos san qui se trovava in contacto con tal patientes. Le studio del documentation relative a ille specimens pare indicar que le clearance del virus de poliomyelitis via le feces de tal excretores seque un curva exponential. Le tempore pro 50% de clearance in le patientes es circa 3 septimanas a partir del declaration del morbo. In le subjectos de contacto, iste tempore es circa 5 septimanas a partir del declaration de symptomas in le patiente in question.

MASSIVE CORTICOSTEROID THERAPY IN THE MANAGEMENT OF RESISTANT THROMBOCYTOPENIC PURPURA

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Patients with persistent or recurring thrombocytopenic purpura present difficult problems in management, particularly if severe bleeding phenomena supervene. This is especially true if the patients fall into one or more of the following categories: (1) those who have not responded to either corticotropin or corticosteroid therapy; (2) those who have not responded to splenectomy; or (3) those who are not considered suitable candidates for splenectomy. The prognosis in these individuals is poor regardless of the etiology of the thrombocytopenia.

It has been observed that extremely large doses of corticosteroids may occasionally produce beneficial effects in disease states such as leukemia and disseminated lupus erythematosus when ordinary amounts are ineffective (Dubois[1], Hill, Marshall and Dalcio[3], Ranney and Gelhorn[6]). It is possible that the failure of some patients to respond to corticosteroid therapy may be due to insufficient dosage. This report deals with the results obtained in treating patients with resistant thrombocytopenic purpura with five to ten times the usual therapeutic amounts of Δ 1 Hydrocortisone (prednisolone).

Materials and Methods. Fourteen patients with resistant thrombocytopenic purpura were treated with 250 to 300 mg. of prednisolone* daily over a period of 7 to 44 days. In most instances the duration of therapy was less than 14 days. Thirteen of the patients had previously failed to respond to ordinary amounts of corticosteroids (100 to 300 mg. of cortisone daily; 30 to 60 mg. of prednisolone daily). The remaining patient (patient 8) was semicomatose on admission and was so severely ill that he was placed immediately on 300 mg. of prednisolone intravenously daily for 11 days.

The platelet count was less than 50,000 per c.mm. in all patients and 10 of the patients had severe hemorrhagic manifestations. Two patients had iodiopathic thrombocytopenic purpura which had not responded to splenectomy. The remaining patients were not considered suitable for splenectomy. These included 2 patients with disseminated lupus erythematosus, 2 with chronic leukemia, 2 with metastatic carcinoma, 3 with aplastic anemia and one each of agnogenic myeloid metaplasia, toxic suppression of the bone marrow, and Hodgkin's disease.

Bone marrow aspiration or surgical biopsy of the marrow was performed on all patients at the beginning of the study period. Platelet counts, by the indirect technique, were obtained daily on all patients. The normal platelet count in our laboratory by this method is 200,000 to 300,000 per c.mm. Attempts were made to demonstrate platelet agglutinins in the serum of all patients using a hemagglutination technique previously described (Suhrland, Arquilla and Weisberger[9]). In

*The prednisolone used in these studies were furnished by the Upjohn Co., Kalamazoo, Michigan.

this method pooled, soluble extracts of human platelets are coated on washed O, Rh-negative erythrocytes with bis-diazo-benzidene. The presence of platelet agglutinins in serum is detected by agglutination of the sensitized erythrocytes and can be titrated by serial dilutions of the serum.

Results. The results are summarized in Table 1. Eight of the 14 patients exhibited an excellent response consisting of a rise in platelets ranging from 300,000 to 850,000 per c.mm. and cessation of hemorrhagic phenomena. The rise in platelet counts became manifest within 3 to 7 days after the beginning of therapy. In the 8 patients who exhibited an excellent response, all but 2 patients had a hyperactive marrow. One of these 2 patients had a marrow infiltrated with lymphocytes of chronic lymphatic leukemia and the other patient had a hypoplastic marrow presumably due to ingestion of a toxic agent.

Only one of these 8 patients (patient 8) continued in good remission following cessation of steroid therapy. It is possible that this patient with a toxic suppression of the marrow might have recovered without steroid therapy. However, it was the opinion of the observers that corticosteroid therapy hastened the rise in the platelet count and that it may have prevented fatal hemorrhage. Four patients relapsed when the prednisolone was gradually discontinued. A fall in the platelet count occurred in 2 patients when maintenance therapy with 100 mg. of prednisolone daily was attempted. The 3 other patients (patients 5, 6, 7) who exhibited a good response initially succumbed to their disease, or a complication of it, while on corticosteroid therapy.

TABLE 1.—THE EFFECT OF LARGE AMOUNTS OF PREDNISOLONE ON THE PLATELET RESPONSE IN PATIENTS WITH RESISTANT THROMBOCYTOPENIC PURPURA

Clinical Diagnosis	*Marrow Activity*	*Platelet Response*
1. ITP (after splenectomy)	Hyperactive	++++
2. ITP (after splenectomy)	Hyperactive	++++
3. Disseminated L–E	Hyperactive	++++
4. Disseminated L–E	Hyperactive	++++
5. Metastatic carcinoma	Hyperactive	++++
6. Chronic lymphatic leukemia	Infiltrated	++++
7. Chronic myeloid leukemia	Hyperactive	++++
8. Toxic suppression of marrow	Hypoactive	++++
9. Aplastic Anemia	Aplastic	0
10. Aplastic Anemia	Aplastic	0
11. Aplastic Anemia	Aplastic	0
12. Metastatic carcinoma	Myelophthisic	0
13. Agnogenic myeloid metaplasia	Fibrotic	0
14. Hodgkin's disease	Infiltrated	0

Six of the 14 patients failed to respond and all 6 had severe marrow depletion or replacement. The 3 patients with aplastic anemia (patients 9, 10, 11) had markedly hypoplastic marrows with absent megakaryocytes. The other 3 patients had marrows heavily involved with either carcinoma, fibrosis or Hodgkin's granuloma.

Toxic manifestations with these large doses of prednisolone were uncommon. Electrolyte imbalance and fluid retention were not a serious problem and in most patients edema formation was not clinically apparent. Mild to moderate Cushingoid facies developed in all pa-

tients, but this was readily reversible when the steroid were discontinued. One patient developed hyperglycemia and glycosuria which subsided when the prednisolone was discontinued. One patient with chronic lymphatic leukemia (patient 6) succumbed to a fulminating B-hemolytic streptococcal infection after receiving large doses of corticosteroids for 55 days. One patient not included in these studies developed tarry stools and epigastric distress after receiving 250 mg. of prednisolone for 2 days, necessitating rapid cessation of therapy.

An immune mechanism could not be implicated in any of the patients. Platelet agglutinins or antibodies were not demonstrated by the techniques used in any of the 14 patients studied. Furthermore, direct addition of prednisolone to rabbit antiserum to human platelets did not inhibit agglutination of erythrocytes coated with platelet extracts.

Cessation of therapy in most patients was accomplished by rapidly decreasing the dosage initially (50 mg. every 2 to 3 days) until ordinary therapeutic amounts were being administered. Further decrease in dosage was then accomplished more gradually. None of the patients were given ACTH and no ill effects were noted.

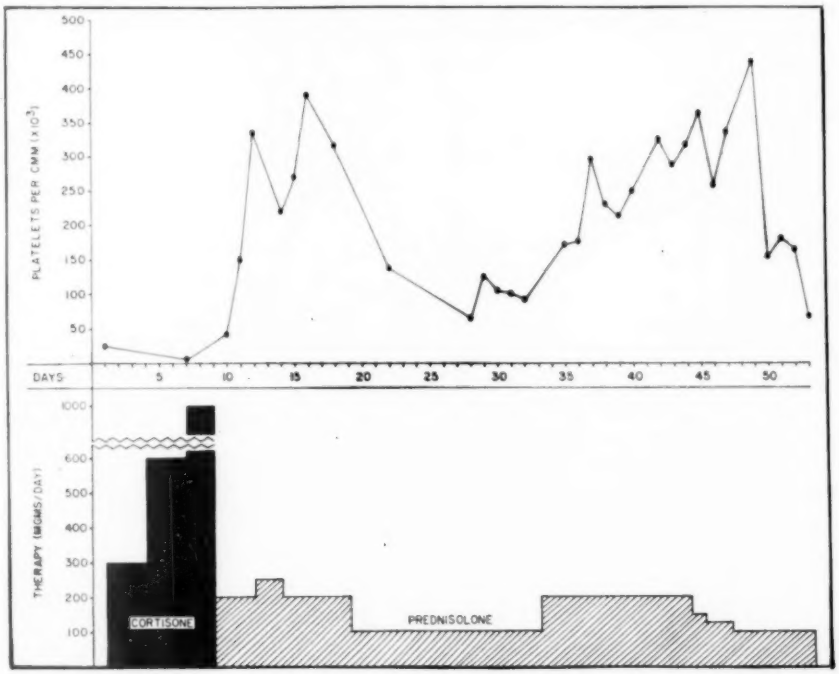

Fig. 1.—Chronic lymphatic leukemia with severe thrombocytopenia treated with large doses of prednisolone. The platelet count rose to normal levels and bleeding phenomena ceased when the patient received 250 mg. of prednisolone daily. The platelet count fell below 100,000 per c.mm. when prednisolone was decreased to 100 mg. daily.

Case Reports. CASE 1.—Chronic Lymphatic Leukemia with severe Thrombocytopenia (Fig. 1):

A 39-year-old Negro woman with known chronic lymphatic leukemia was admitted to University Hospitals of Cleveland with severe purpura, epistaxis and gastro-

intestinal bleeding. The initial platelet counts ranged between 3,000 and 25,000 per c.mm. The bone marrow was heavily infiltrated with lymphocytes and no megakaryocytes were seen. She was placed on cortisone, 100 mg. t.i.d., and after 3 days this was increased to 600 mg. and then 1000 mg. daily for the next 6 days because of continuous severe bleeding. The platelet count remained low and the abnormal bleeding persisted. Cortisone was discontinued and 250 mg. of prednisolone was given daily. In 3 days the platelet count had risen to 340,000 per c.mm. with a subsequent rise to 400,000 per c.mm. When prednisolone was decreased to 100 mg. daily, the platelet count fell to 75,000 per c.mm. Each time prednisolone was reduced, the platelet count would fall and severe bleeding would recur. After 55 days of massive corticosteroid therapy daily, the patient developed a fatal overwhelming infection with B-hemolytic streptococcus.

COMMENT. The rise in platelet count to normal levels in this patient was surprising in view of the absence of megakaryocytes in the bone marrow aspirate. The failure to demonstrate megakaryocytes may have been due to a sampling error, however, platelet production may have occurred at other sites. It is evident that large doses of prednisolone maintained the platelet count at a normal level when ordinary therapeutic amounts of corticosteroids were ineffective. The type of corticosteroid employed may be a factor, since 1000 mg. of cortisone was ineffective over a 6-day period. It is possible, however, that the extremely high dose of cortisone might have produced the desired effect if it had been continued for a longer interval.

The large amount of corticosteroids administered over a 2-month period undoubtedly contributed to the overwhelmingly fatal infection. This type of therapy should, therefore, be reserved for emergencies only.

CASE 2.—Idiopathic Thrombocytopenic Purpura with failure of Splenectomy (Fig. 2):

A 68-year-old white woman was first seen in June, 1955, with a low platelet count and purpura. Bone marrow examination was compatible with the clinical diagnosis of idiopathic thrombocytopenic purpura and splenectomy was performed in July, 1955. The platelet count failed to rise and the patient was placed on cortisone, 100 mg. daily. There was no significant change in circulating platelet counts. One year later, she was readmitted to the hospital because of a severely prolapsed uterus. Although her platelet count at this time was 9,840 per. c.mm., surgical correction of the prolapsed uterus was desirable. She was given prednisolone, 300 mg. daily, and the platelet count rose to 315,000 per c.mm. A vaginal hysterectomy was performed without abnormal bleeding and the convalescence was uncomplicated. Postoperatively the platelet count rose to 786,000 per c.mm. and then gradually fell to 150,000 per c.mm. as the prednisolone was slowly reduced. She continued to do well and is asymptomatic at the present time with a platelet count ranging between 75,000 and 100,000 per c.mm.

COMMENT. In this instance large doses of prednisolone produced a rise in platelet count not obtained with a therapeutic dose of cortisone and made it possible to perform required major surgery. Wound healing was not impaired in spite of the massive corticosteroid therapy. The platelet count fell to the previous subnormal level when corticosteroid therapy was discontinued.

CASE 3.—Idiopathic Thrombocytopenic Purpura with failure of splenectomy (Fig. 3):

This patient was a 45-year-old white woman who was referred to University Hospitals of Cleveland because of purpura, epistaxis and profuse uterine bleeding. Two years previously, she had had a splenectomy for idiopathic thrombocytopenic purpura without benefit and the platelet count had remained low. Two weeks before admission she had been placed on 200 mg. of cortisone daily. On admission her platelet count was 23,500 per c.mm., the bleeding time was prolonged and clot retraction was absent. Cortisone was discontinued and she was given 60 mg. of prednisolone daily. After 2 weeks with no significant change in platelet count and persisting hemorrhage, the dosage of prednisolone was increased to 250 mg. daily. Within 9 days the platelet count had risen to 594,500 per c. mm. and the bleeding phe-

nomena subsided. Subsequently, the prednisolone dosage was reduced, resulting in a concomitant fall in platelet count. She continued to manifest chronic thrombocytopenia with frequent epistaxis and purpura.

COMMENT. This patient with chronic thrombocytopenic purpura who failed to respond to splenectomy was able to respond with a marked rise in platelets on large doses of prednisolone. The usual therapeutic amounts of prednisolone were ineffective, and the platelet count fell to the previous low levels when the dose of prednisolone was decreased. Temporary administration of massive corticosteroid therapy was effective in controlling the serious hemorrhagic phenomena.

CASE 4.—Aplastic Anemia (Fig. 4): This patient, a 52-year-old white woman, entered the hospital with purpura and was found to have an anemia, leukopenia and thrombocytopenia. A bone marrow section showed a markedly hypoactive marrow. She was given 400 mg. of cortisone daily without benefit. She was then changed to 250 mg. of prednisolone daily. No rise in platelets occurred after 10 days and the prednisolone was gradually reduced.

COMMENT. This case represents the typical response in patients who have marrows that are depleted or replaced.

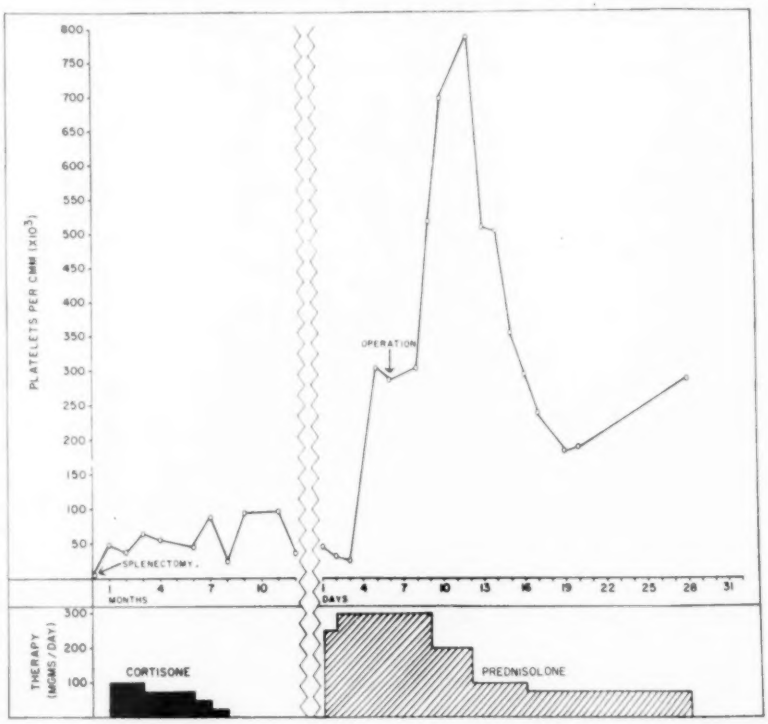

Fig. 2.—Idiopathic thrombocytopenic purpura persisting after splenectomy treated with large doses of prednisolone. The platelet count remained low after splenectomy and did not respond to 100 mg. of cortisone daily over a period of several months. Within 4 days of receiving 300 mg. of prednisolone daily the platelet count rose to normal levels and an elective operative procedure was performed without difficulty.

Thus a potential source for platelet production must be present before a response to massive therapy can be anticipated.

Discussion. The results demonstrate that in certain patients with thrombocytopenic purpura large doses of prednisolone can produce a rise in platelet count and a cessation of bleeding phenomena when ordinary therapeutic doses of corticosteroids are ineffective. The most important factor in achieving a desirable result appears to be the presence of adequate numbers of megakaryocytes in the marrow. The absence of demonstrable megakaryocytes in the marrow does not necessarily rule out the possibility of a good response because of sampling errors inherent in the technique of marrow aspiration as well as the possibility that megakaryocytes may be present in extramedullary sites. Most of the failures in this series of observations occurred in patients with aplastic or myelophthisic marrows.

Although splenectomy is effective in 60 to 70% of patients with idiopathic thrombocytopenic purpura (Learmonth[4], Lozner[5], Stefanini and Dameshek[7]), the patients who fail to receive benefit often continue to manifest hemorrhagic phenomena. These hemorrhagic phenomena are potentially dangerous and may present problems in management particularly if severe bleeding supervenes or surgery is required. The response of 2 such patients to massive steroid therapy when ordinary doses were ineffective, indicates that these patients are capable of producing a rise in platelets to normal levels despite the continued operation

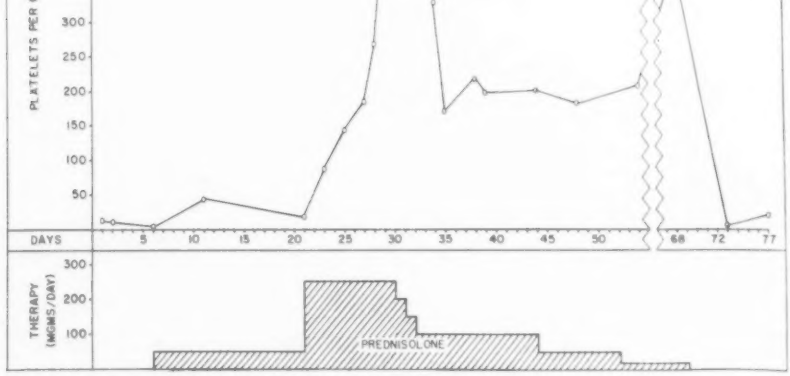

Fig. 3.—Chronic thrombocytopenic purpura persisting after splenectomy and not responding to ordinary therapeutic doses of prednisolone. With massive prednisolone therapy the platelet count rose to a high level and dangerous bleeding phenomena were controlled. The platelet count fell to the previous low level as the dosage of prednisolone was decreased to ordinary therapeutic amounts.

of a poorly understood pathologic mechanism.

In patients in whom splenectomy for thrombocytopenia is contraindicated, the availability of the corticosteroids has been extremely helpful in many instances. When these patients fail to respond to ordinary therapeutic amounts of corticosteroids, it may be difficult to control bleeding phenomena. The response to massive therapy in 6 of 12 such patients again demonstrates that corticosteroids in sufficient dosage can produce a beneficial effect even in the presence of a continuing pathological process.

The lack of response in patients with aplastic or myelophthisic marrows to massive corticosteroid therapy is not surprising. A response in such patients would not be expected, except perhaps in the presence of extramedullary hematopoiesis. The lack of response in a patient with agnogenic myeloid metaplasia suggests that increased production from extramedullary sites may not be sufficient to counteract increased destruction.

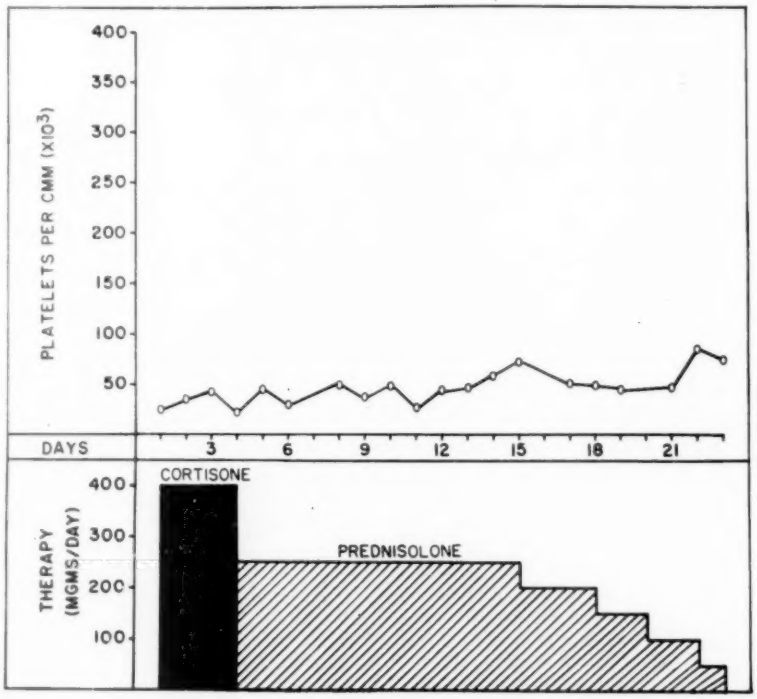

Fig. 4.—Patient with aplastic anemia not responding to massive corticosteroid therapy.

The mechanism by which massive corticosteroid therapy produces a response not obtainable with ordinary doses, is not known. It may be postulated that both decreased destruction and increased production of platelets may be factors in producing improvement. The prompt response within 3 to 7 days is compatible with both of these processes. There is some indication that

decreased destruction may be more important than increased production. This is based on the observation that 2 patients without thrombocytopenia (acute rheumatic fever and multiple sclerosis) who received large doses of corticosteroids did not exhibit a significant rise in platelet count.

It has frequently been suggested that immune mechanisms are involved in the production of certain thrombocytopenic states (Harrington[2] Stefanini *et al.*[8]). Although no platelet agglutinins or platelet antibodies were demonstrated in these patients using a hemagglutination technique, prednisolone may decrease platelet antibody formation. In the experimental production of antibodies in rabbits to human platelets, almost complete suppression of antibody formation can be obtained by large amounts of corticosteroids (Suhrland, Arquilla and Weisberger[9]).

It is possible then that in those patients who responded, inhibition of formation of an anti-platelet factor by sufficient amounts of corticosteroids may be responsible for the rise in circulating platelets.

Complications inherent in the use of corticosteroids are even more likely to occur with the doses employed in these studies. Such treatment is obviously not suitable for prolonged periods or for maintenance therapy. The risks involved, however, are quite acceptable for emergency use when continuous bleeding threatens life or when surgery is urgently required in patients with severe thrombocytopenia. In several patients in this series, such bleeding was successfully treated temporarily with large doses of prednisolone. The use of massive therapy as preoperative preparation for elective surgery would be a calculated risk and requires individual evaluation. The uneventful course of one such patient (Case 2) suggests that this approach is feasible.

It is to be re-emphasized, that massive therapy is indicated only in special circumstances and is not suited for routine use or maintenance. Patients receiving such large doses of corticosteroids must be observed carefully for gastrointestinal bleeding, infection, retention of fluids and electrolyte imbalance. In this present series, one patient developed an overwhelming infection after 55 days of therapy and died. There were no other serious side-effects and electrolyte disturbance and fluid retention were not a problem in the patients studied. This was in part due to the choice of a corticosteroid with minimal mineralocorticoid effect.

Summary. 1. In certain patients with resistant thrombocytopenic purpura large doses of prednisolone can produce a rise in platelet count and a cessation of bleeding phenomena when ordinary therapeutic doses of corticosteroids are ineffective.

2. The presence of adequate numbers of megakaryocytes in the bone marrow is essential for this effect in most instances.

3. The platelet count usually returns to thrombocytopenic levels when the dosage of corticosteroids is reduced to ordinary therapeutic levels.

4. Complications attributable to the large doses of prednisolone used in these studies were uncommon. However, therapy with massive doses of corticosteroids should be reserved for acute emergencies rather than for maintenance therapy.

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SUMMARIO IN INTERLINGUA

Therapia A Corticosteroide Massive In Le Tractamento De Resistente Purpura Thrombocytopenic

1. In certe patientes con resistente purpura thrombocytopenic, grande doses de prednisolona pote effectuar un augmento del numeration plachettal e un cessation del phenomenos de sanguination quando le ordinari doses therapeutic de corticosteroides es inefficace.

2. In le majoritate del casos, le presentia de numeros adequate de megacaryocytos in le medulla ossee es necessari pro le production de iste effecto.

3. Le numeration plachettal retorna usualmente a nivellos thrombocytopenic quando le dosage de corticosteroide es reducite al ordinari nivellos therapeutic.

4. Complicationes attribuibile al massive doses de prednisolona usate in iste studios esseva incommun. Tamen, therapia a doses massive de corticosteroides deberea esser reservate pro situationes de urgentia acute e non es a recommendar in le therapia de mantenentia.

THE ANGIOCARDIOGRAPHIC FEATURES OF A PATENT FORAMEN OVALE*

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We have previously reported in this journal the pathognomonic angiocardiographic findings in interatrial septal defects of the ostium secundum and ostium primum types[1]. We herein describe the pathognomonic angiocardiographic features of a patent foramen ovale.

Case Report. M.T., a 14-year-old Negress, was referred to Temple University Hospital by her school teacher because of shortness of breath upon effort which was present for a long time and was increasing. She was otherwise asymptomatic.

Examination revealed a precordial systolic murmur loudest in the pulmonic region where it was blowing in character and grade 4 in intensity. P_2 was decreased in intensity. Examination was otherwise unremarkable. The blood pressure was 110/60 mm. Hg.

Routine laboratory studies, including a blood count, serology and urinalysis, were normal.

Electrocardiogram disclosed sinus rhythm and findings indicative of right ventricular hypertrophy. The P vector was increased in magnitude and directed 60 degrees anteriorly. The QRS vector was directed 135 degrees anteriorly. In lead V_1, the R wave was 24 mm. in amplitude and the T wave was asymmetrically inverted.

Conventional roentgenographic examination of the chest revealed a markedly convex pulmonary artery segment. There was no increase in the over-all size of the cardiac silhouette. The vascular markings were essentially normal. There was no pulmonary parenchymal abnormality.

The data obtained by cardiac catheterization were as follows:

	Pressure (mm. Hg)	*Oxygen Content (Volumes %)*
Superior vena cava	2/—5	10.4, 10.7
Right atrium	2/—5	11.2, 10.8
Right ventricle	102—155/0	10.3, 10.9
Pulmonary artery	16/2	10.3

The systemic arterial oxygen saturation was 90% on one occasion and 86% on another.

Venous angiocardiography was done using the Chamberlain biplane stereoscopic angiocardiographic apparatus. Thirty milliliters of 70% Urokon were injected rapidly into the right antecubital vein which was cannulated with a Robb-Steinberg needle. Roentgenograms were obtained simultaneously in the posterior-anterior and left lateral projections every 0.7 second for a total of 30 frames. The duration of each exposure was 0.1 second.

The degree and duration of opacification of the great vessels and cardiac chambers were determined from the sequential angiocardiograms by the method previously described[2]. The flow sheet is shown in Fig. 1.

The intracardiac circulation time, that is, the time from the initial appearance of opacity in the right atrium to that in the ascending aorta, is 5.6 seconds (normal is 6.3 seconds). The duration of opacification of the superior vena cava is 4.2 seconds, that of the right heart 5.6 seconds and that of the pulmonary artery 6.3 seconds, all within the limits of normal.

Upon opacification of the right atrium, a

*Supported in part by a grant from the Heart Association of Southeastern Pennsylvania.

small amount of contrast substance was seen in the adjacent upper part of the left atrium in the lateral projection. This density quickly faded and disappeared. There was no filling defect in the right atrium by nonopacified left atrial blood and the right atrium was not re-opacified when the left atrium was opacified. Characteristic angiocardiograms are shown in Fig. 2.

The superior vena cava and right atrium did not appear to be enlarged. The right ventricle was hypertrophied. The pulmonary artery was huge. A jet of contrast substance from the right ventricle was seen in the pulmonary artery. The left atrium and ventricle were not enlarged. The aorta was small.

On the basis of these findings, a diagnosis was made of pulmonary valvular stenosis and patent foramen ovale with right to left flow.

At surgery, the pulmonary artery was found to be greatly dilated. A coarse thrill was felt through the soft pulmonary artery and a forceful jet was felt upon its wall several centimeters distal to the valve. A number 13 sound was the largest that could be passed through the pulmonary valve from below. A Brock procedure was done and the postoperative course was uneventful.

Discussion. Cardiac septal defects, regardless of location, can be specifically recognized by biplane stereoscopic venous angiocardiography. Characteristically, with left to right flow, the intracardiac circulation time is rapid and the duration of opacification of the right side of the heart is prolonged.

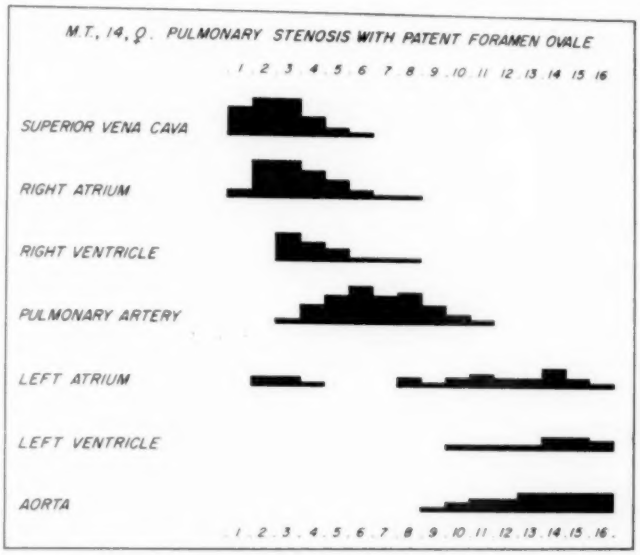
M.T., 14, ♀. PULMONARY STENOSIS WITH PATENT FORAMEN OVALE
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
SUPERIOR VENA CAVA
RIGHT ATRIUM
RIGHT VENTRICLE
PULMONARY ARTERY
LEFT ATRIUM
LEFT VENTRICLE
AORTA
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

Fig. 1.—Degree and duration of opacification of the great vessels and cardiac chambers. Notice the early appearance of opacity in the left atrium due to opacified right atrial blood. Later, left atrial opacity re-appears but is not intense probably because of dilution by nonopacified right atrial blood. No left to right shunt is present.

Owing to increased flow, the aorta is opacified quickly and owing to recirculation from the left heart, the right heart remains opacified for a long time. The right atrium and right ventricle show prolonged opacification with an interatrial septal defect and the right ventricle alone with an interventricular septal defect. Such findings are strongly suggestive of septal defects with left to right flow but are not diagnostic. The pathognomonic

finding is re-opacification of the right side by opacified blood from the left side. With an interatrial septal defect, the right atrium is re-opacified by opacified left atrial blood and with an interventricular septal defect, the right ventricle is re-opacified by opacified left ventricular blood[3]. The ostium primum type of interatrial septal defect can be distinguished from the other types by its caudal location and also by opacification of the left ventricle by opacified right atrial blood[1].

In contrast with these findings, there is no left to right flow through a patent foramen ovale. It is anatomically open

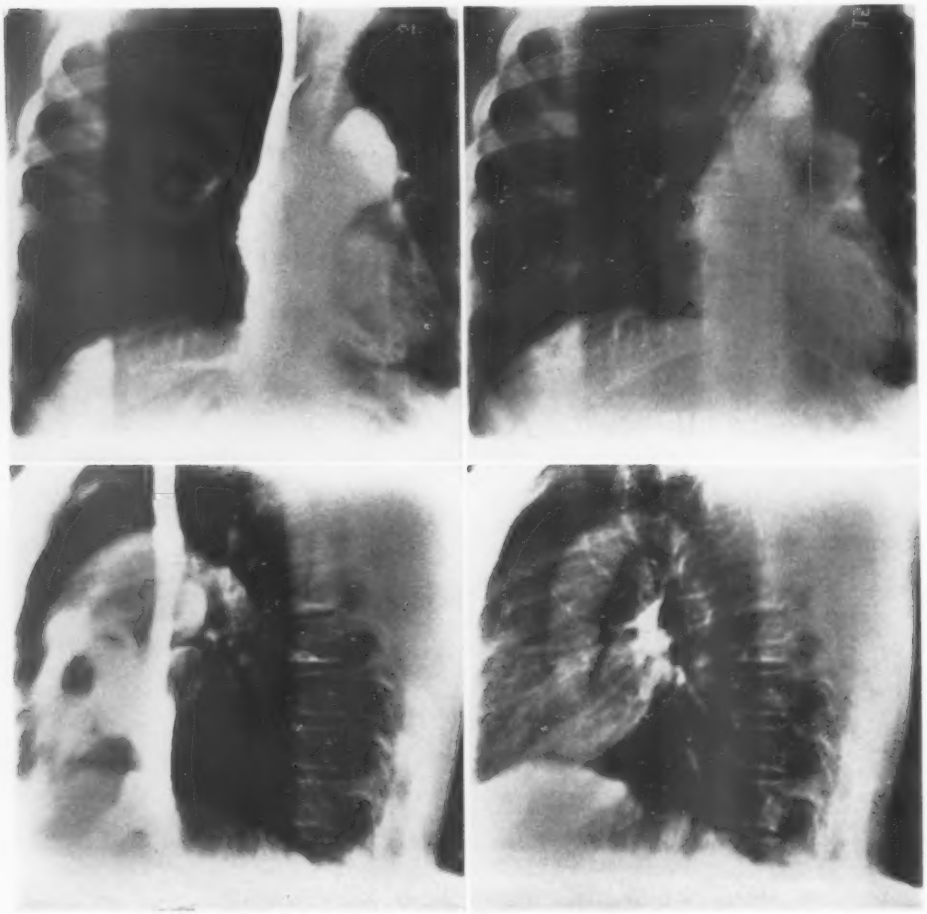

Fig. 2.—Angiocardiograms in the posterior-anterior (above) and left lateral (below) projections obtained simultaneously at 0.7 second (left) and at 9.8 seconds (right) after initial appearance of opacity in the right atrium. The angiocardiograms on the left demonstrate opacification of the superior vena cava, right atrium, right ventricle and pulmonary artery. There is reflux opacification of the inferior vena cava and hepatic veins. Notice, in the lateral projection, contrast substance in the upper part of the left atrium adjacent to the right atrium. Notice also the absence of mixing defects in the right atrium. A jet of contrast substance is seen in the huge pulmonary artery. The later angiocardiograms demonstrate opacification of the left atrium, left ventricle and aorta. No contrast substance reappears in the right atrium

but functionally closed because its valve is on the side of the left atrium whose pressure exceeds that of the right atrium. Therefore, flow through a patent foramen ovale with a competent valve can occur only from right to left and then only when the hemodynamic conditions are appropriate.

When contrast substance is rapidly and forcibly injected, the right atrial pressure may become transiently elevated to a degree sufficient to force blood through the foramen ovale from right to left. The elevated right atrial pressure is quickly dissipated and the opening is quickly closed. Angiocardiography, under such circumstances, will demonstrate a right to left shunt and no left to right shunt. The amount of contrast substance entering the left atrium from the right atrium is usually inadequate to produce opacification of the entire left atrium or the aorta, because the defect is small and the shunt transient. More shunting from right to left may occur if resistance offered by the patent foramen ovale and left atrium is less than that of the right ventricle. Opacity in the left atrium, after its early appearance from the right atrium, may fade and never become intense because of subsequent dilution by nonopacified right atrial blood. Again, however, the patent foramen ovale is distinguished from an interatrial septal defect by the absence of any left to right flow. There is neither a mixing defect in the right atrium by nonopacified left atrial blood nor re-opacification of the right atrium by opacified left atrial blood. If left to right flow through an interatrial septal defect of the ostium secundum type cannot be recognized because of cardiac size or prolonged circulation times, differentiation from a patent foramen ovale may be impossible.

Left to right flow through a patent foramen ovale is possible only if its valve is incompetent. Under such circumstances cardiac enlargement is present and the foramen ovale is functionally identical and anatomically similar to an interatrial septal defect of the ostium secundum type. In the absence of cardiac enlargement, the demonstration of left to right interatrial flow excludes a patent foramen ovale.

Summary and Conclusions. 1. The angiocardiographic findings of a patent foramen ovale are described.

2. The pathognomonic finding is the demonstration of opacity in the left atrium due to opacified right atrial blood in the presence of otherwise normal angiocardiographic circulation times and in the absence of mixing defects in the right atrium by nonopacified left atrial blood.

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SUMMARIO IN INTERLINGUA

Characteristicas Angiocardiographic De Un Patente Foramine Oval

1. Es describite le constatationes angiocardiographic in un caso de patente foramine oval.

2. Le signo pathognomonic es opacitate in le atrio sinistre causate per opacificate sanguine dextero-atrial in le presentia de alteremente normal tempores circulatori angiocardiographic e in le absentia de defectos de mixtion in le atrio dextere per non-opacificate sanguine sinistro-atrial.

ACUTE HEPATIC CONGESTION AS A FACTOR IN ELEVATED SERUM GLUTAMIC OXALOACETIC TRANSAMINASE TITERS ABOVE 400 UNITS

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Much has been written concerning the rise in serum levels of glutamic oxaloacetic transaminase following myocardial infarction, first described by LaDue, Wroblewski, and Karmen[1] in 1954. Since GOT is present in all human sera and in various tissues, particularly heart muscle, liver, skeletal muscle, and kidney (in descending order of concentration), sufficient necrosis of any of the above may cause a rise in enzyme (SGOT) levels. The SGOT unit-time curve, in addition to the peak level of the enzyme, has been shown to be of diagnostic value in differentiating chemically where the cell death has occurred; for example, in pulmonary infarctions, there is a delayed rise in SGOT levels until the fourth day after the onset of symptoms, the titer rarely exceeding 65 u. per ml., in contrast to the sharp rise in SGOT within an average of 26 hours (2 to 96 hours) in acute myocardial infarction[2]. Ostrow, Steinberg, Ticktin, Polis, and Evans[2], in a review of 60 cases of acute transmural myocardial infarction, reported a peak value of 375 units attained. The same group reported that normal levels (below 40 u. per ml.) were observed in uncomplicated cardiac failure, pneumothorax, and nephrosis with edema. Studying SGOT titers in liver disease, Wroblewski, Jervis, and LaDue[4] reported in infectious hepatitis a peak of 2500 units, in infectious mononucleosis complicated by hepatitis a peak of 300 units, in compensated cirrhosis a normal SGOT, in decompensated or active cirrhosis 300 units, extrahepatic biliary cirrhosis a peak of 300 units, and in primary hepatoma or hepatic metastases a peak of 250 units.

Interest in unusually high transaminase levels and their possible association with acute congestive hepatomegaly was generated by the finding of an SGOT titer of 3000 units in a patient with acute congestive failure without myocardial infarction or hepatitis.

Material and Methods. An analysis of all patients in this general hospital having an SGOT titer of greater than 400 units was made. Out of a total of more than 1900 SGOT determinations made in this hospital since October, 1956, there were 29 patients who had at least one SGOT determination greater than 400 units. The charts of these patients were analyzed with particular attention directed toward:

1. History: Substernal pain, symptoms of acute *vs.* chronic congestive heart failure, liver pain, or other hepatic symptoms.
2. Physical Examination: Cardiac and chest pathology, liver tenderness, liver enlargement, peripheral edema, pulmonary edema, and shock. Only when consistent mention of an enlarged tender liver was made, or when one of the authors had observed definite liver tenderness or right upper quadrant tenderness or a rapid change in liver size, or any combination of these, was acute congestion of the liver deemed

to have occurred. On many of the charts examined, the upper border of hepatic dullness was not noted and so liver size cannot be stated definitely. Despite this limitation and despite the fact that the evaluation of slight liver enlargement may be difficult, as much objectivity as possible was used in the clinical determination of liver size.

3. Electrocardiograms: For unequivocal evidence of myocardial infarction, or an absence of such evidence.
4. Liver Function Studies: For evidence of acute hepatocellular damage or other liver functional impairment.

Table 1 presents the information available in this study.

Results. In the series of 29 patients having one or more SGOT levels greater than 400, there were 8 cases of primary liver pathology with a transaminase range between 490 and 2150 units, the average being 1027 units. There were 2 deaths in the group. This group is discussed in detail elsewhere (Wroblewski, Jervis and LaDue[4]), and will be omitted from further discussion.

The remaining 21 cases were divided as follows:

1. Three cases which exhibited *acute congestive hepatomegaly without clinical or electrocardiographic evidence of myocardial infarction.* These patients all presented with enlarged tender livers and other signs of acute congestive failure, for example, pulmonary edema. The SGOT titers in these patients ranged from 700 to 3000 units with an average of 1510. One death occurred in this group. A.G., No. 1, Table 1 was admitted in acute congestive failure with pulmonary edema, shock, peripheral edema, and enlarged tender liver due to decompensated rheumatic heart disease. The SGOT titer was 3000 units. Postmortem examination attributed death to aspiration of blood from hemorrhage originating from a chronic duodenal ulcer. The liver showed gross and microscopic evidence of long standing passive congestion with additional central lobular necrosis attributed to the superimposed acute passive congestion and hypoxia. There was no evidence of hepatic disease other than congestion. No other gross or microscopic findings of the postmortem examination could explain the extremely high SGOT titer.

   A second patient in this group, V.S., No. 2, Table 1, (SGOT 830 units) was adequately treated for her rheumatic heart disease with acute congestive failure, but expired 5 months later during aortic valvular surgery. Postmortem examination revealed neither gross nor microscopic evidence of myocardial infarction. The liver showed dilatation of the central veins with slight compression atrophy in the central zones. No other signs of tissue damage other than recent changes attributed to her death could be found.
2. Nine cases exhibiting definite clinical and electrocardiographic evidence of *acute myocardial infarction and acute passive congestion of the liver.* The peak SGOT titers in this group ranged from 430 to 2050 with an average of 886. In this group, there were 6 deaths (67% mortality), and 7 of 9 patients had their clinical course complicated by shock. By way of illustration, gross and microscopic postmortem examination of B.R., age 76, No. 9, Table 1, revealed an extensive anteroseptal myocardial infarction with marked passive congestion of the liver; however, there was no necrosis. No other tissue necrosis could be found.
3. Nine cases exhibiting definite clinical and electrocardiographic evidence of acute myocardial infarction

TABLE 1.—SUMMARY OF EXPERIMENTAL DATA AVAILABLE IN PATIENTS WITH AN SGOT GREATER THAN 400 UNITS

All patients had electrocardiograms which were diagnostic of myocardial infarction or showed no evidence of infarction. The eight cases with primary liver pathology are not listed.

Group	*No.*	*Init.*	*Age*	*Final Diagnosis*	*Evidence of Liver Involvement*	*Cause of Liver Involvement*	*Shock*	*Symptomatic Days Before Start of SGOT Series*	*Transaminase Series*				*Disposition*	*Necropsy*
									Day 1	*Day 2*	*Day 3*	*Day 4*		
1	1	A.G.	45	Rheumatic Heart Disease with Acute Pulmonary Edema and Peptic Ulcer (Hepatic Congestion)	Tender Enlarged 3 cm. below RCM	Passive Congestion	Yes	2	3000	Died	——	——	Died	Hepatic Central Lobular Necrosis, Rheumatic Heart Disease with Mitral Insufficiency and Aortic Insufficiency
1	2	V.S.	39	Rheumatic Heart Disease with Acute Pulmonary Edema (Hepatic Congestion)	Sudden Enlargement to 3 cm. below RCM	Passive Congestion	No	4	830	←11 Days→		75	Discharged	Necropsy 4 mos. later showed no evidence of Myocardial Infarction
1	3	W.H.	80	Hypertensive Cardiovascular Disease with Acute Pulmonary Edema (Hepatic Congestion)	Tender Enlarged 4 cm. below RCM	Passive Congestion	No	2	700	200	——	——	Discharged	——
2	4	M.G.	75	Acute Myocardial Infarction (Hepatic Congestion)	Tender Enlarged 2 cm. below RCM	Passive Congestion	Yes	2	485	245	80	——	Died	No Necropsy

♀	5	A.S.	69	Acute Myocardial Infarction (Hepatic Congestion)	Tenderness in Epigastrium and Right Upper Quadrant	Passive Congestion	No	1	65	650	525	Died	Died	No Necropsy
♀	6	R.C.	71	Acute Myocardial Infarction with Pulmonary Edema (Hepatic Congestion)	Tender Enlarged 2 cm. below RCM	Passive Congestion	Yes	1	1200	2050	1350	Died	Died	No Necropsy
♀	7	A.D.	82	Acute Myocardial Infarction with Pulmonary Edema (Hepatic Congestion)	Tender Enlarged 3 cm. below RCM	Passive Congestion	Yes	2	1000	Died	——	——	Died	No Necropsy
♀	8	L.S.	71	Acute Myocardial Infarction (Hepatic Congestion)	Tender Enlarged 3 cm. below RCM	Passive Congestion	No	1	72	510	420	250	In Hospital	——
♀	9	B.R.	76	Acute Myocardial Infarction (Hepatic Congestion)	Enlarged 4 cm. then 2 cm. below RCM	Passive Congestion	Yes	1	130	320	900	700	Died	Anteroseptal Infarct, Hepatic Passive Congestion
♀	10	L.G.	63	Acute Myocardial Infarction (Hepatic Congestion)	Epigastric and Right Upper Quadrant Tenderness	Passive Congestion	Yes	? (3+)	430	270	——	40	Discharged	——
♀	11	I.K.	61	Acute Myocardial Infarction (Hepatic Congestion)	Severe Right Upper Quadrant and Epigastric Tenderness	Passive Congestion	Yes	1	152	700	1150	400	Died	No Necropsy

TABLE 1.—SUMMARY OF EXPERIMENTAL DATA AVAILABLE IN PATIENTS WITH AN SGOT GREATER THAN 400 UNITS—(*Continued*)

Group	*No.*	*Init.*	*Age*	*Final Diagnosis*	*Evidence of Liver Involvement*	*Cause of Liver Involvement*	*Shock*	*Symptomatic Days Before Start of SGOT Series*	*Transaminase Series*				*Disposition*	*Necropsy*
									Day 1	*Day 2*	*Day 3*	*Day 4*		
2	12	H.S.	68	Acute Myocardial Infarction (Hepatic Congestion)	Enlarged 1 cm. below RCM Slightly Tender	Passive Congestion	Yes	1	38	800	520	46	Discharged	——
3	13	R.S.	55	Acute Myocardial Infarction	0	0	No	1	675	580	——	——	Discharged	——
3	14	H.P.	52	Acute Myocardial Infarction	0	0	Yes	1	550	——	400	60	Discharged	——
3	15	W.S.	72	Acute Myocardial Infarction	0	0	No	1	480	170	83	21	Discharged	——
3	16	S.K.	82	Acute Myocardial Infarction with Perforation of Interventricular Septum	0	0	Yes	2	300	480	108	——	Died	Anteroseptal Infarct with Septum Perforation, Liver Normal
3	17	H.K.	69	Acute Myocardial Infarction	0	0	No	2	400	——	——	——	Discharged	——
3	18	C.C.	44	Acute Myocardial Infarction	0	0	No	2	495	260	84	42.5	Discharged	——
3	19	N.T.	63	Acute Myocardial Infarction	0	0	No	1	210	225	400	320	Discharged	——
3	20	T.B.	69	Acute Myocardial Infarction	0	0	No	1	180	425	200	——	Discharged	——
3	21	J.H.	54	Acute Myocardial Infarction	0	0	No	1	375	430	350	——	Discharged	——

without clinical evidence of an enlarged or tender liver. In this group the peak SGOT titer ranged from 400 to 675 with an average of 482. Clinical shock complicated the course of 2 of these patients. One death occurred in this group, S.K., No. 16, Table 1. Postmortem gross and microscopic examination revealed only a recent myocardial infarction with interventricular septal perforation. The liver was normal sized and showed no signs of passive congestion.

Discussion. From the available data it would appear that in the absence of infarction or other hepatic disease, acute hepatic congestion, *per se*, can cause sufficient hepatocellular alteration to elevate the SGOT titer. Certainly when chronic passive congestion has damaged the liver, a superimposed acute episode of congestion may cause hepatocellular death as revealed by the postmortem findings in case No. 1, Table 1. The magnitude of the "hepatic congestion factor" in causing a rise in the SGOT titer is illustrated by a comparison of the titers in uncomplicated myocardial infarction (Group III, 9 cases) and those cases with hepatic congestion both with and without myocardial infarction (Groups I and II, 12 cases). The average SGOT titer in uncomplicated myocardial infarction in this series was 482 units compared with an average value in the presence of hepatic congestion of 1042 units.

Histologically, either hepatocellular necrosis (Group I, case 1) or hepatic passive congestion with intact cellular structure (Group II, case 9) may be seen. Highest SGOT titers, in this series, occurred with hepatic necrosis, but evidently hepatic injury, to a point short of necrosis, can cause a rise in SGOT titers. The histochemical physiology is not known, but presumably the factor of hypoxia or elevated hepatic venous pressure or both are responsible for the hepatocellular changes which give rise to the elevated enzyme level. It is well recognized, however, that on histological grounds, it is impossible to determine which damaged cell will die or which will recover. It is probably correct to say that it is the rare case of acute hepatic congestion where the hypoxia or mechanical factors are sufficient to cause hepatocellular necrosis.

In further analysis of the unit-time curves of SGOT titers in Groups I, II, and III, it was found that with the exception of 2 cases who expired on the first day of the series Nos. 1 and 7), all of the titers were declining. This would indicate that the release of enzyme had ceased and that the hepatocellular changes reflected in the SGOT titers had not been a continuing process even though death did not occur for as long as 10 days after the titers were determined. From these facts it may be concluded that the hepatocellular changes resulting in excessively high SGOT titers were not of themselves the primary reason for death, but merely a reflection of the severity of the underlying disease process responsible for the congestion.

Not infrequently patients with uncomplicated myocardial infarction have SGOT titers in excess of 400 units. The range of the 9 cases in this series was 400 to 675 units. No correlation between the height of the titer and the amount of damage to the myocardium can be made from this study. The only patient who died in Group III (SGOT 480) showed an acute anteroseptal myocardial infarction with perforation of the interventricular septum and no gross or microscopic evidence of cellular changes in the liver, brain, or kidneys. An unusually high SGOT titer in an uncomplicated myocardial

TABLE 2.—SUMMARY OF RESULTS

Group Number	*Diagnosis*	*Number of Cases*	*Average SGOT Titers*	*Range of SGOT Titers*	*Number of Deaths*	*% Deaths*
I	Acute Hepatic Congestion without Hepatitis or Myocardial Infarction	3	1510	700 to 3000	1	33%
II	Acute Myocardial Infarction with Clinical Evidence of Liver Congestion	9	886	430 to 2050	6	67%
III	Acute Myocardial Infarction without Liver Congestion	9	482	400 to 675	1	11%
IV	Primary Liver Pathology (A) Infectious Hepatitis 6 cases-all survived (average 700 units) (B) Decompensated Cirrhosis (in coma) 2 cases, both died	8	1027	490 to 2150	2	25%

infarction (without liver involvement) did not seem to alter the prognosis.

In contrast to the above, the short term prognosis was extremely poor (6 deaths, 67% mortality) in the 9 patients whose myocardial infarction was complicated by clinically apparent congestion of the liver (SGOT titers ranging from 430 to 2050, average 886). Furthermore, peripheral circulatory collapse complicated the clinical course of 7 of the 9 patients (79%), compared to the occurrence of shock in the uncomplicated infarction group (22%) and the acute hepatic congestion group (33%). Whereas the absolute SGOT titer (unless very high) cannot be used as a diagnostic index of acute hepatic congestion because of the overlapping of ranges, the finding in a patient with a myocardial infarction of a SGOT titer in excess of 600 to 650 units should make one suspicious of severe hepatic congestion.

Passing mention might be made of the extreme difficulty experienced in the control of prothrombin time in several patients with acute liver congestion treated with antiprothrombin anticoagulants. It was believed that hepatic congestion was the factor making control difficult (Shields and Shannon[3]).

Summary. An analysis of SGOT titers greater than 400 units led to the following conclusions:

1. Acute hepatic congestion can cause elevated SGOT titers. When the congestion is severe, high titers above 500 can result; where the congestion is severe enough to cause hepatic necrosis, titers up to 3000 units may occur.

2. The importance of the "hepatic congestion factor" in SGOT titers (above 400 units) is emphasized by the significant difference of the average titer in uncomplicated myocardial infarctions (482) and the average titer in all cases of acute hepatic congestion (1042), irrespective of etiology.

3. Not infrequently, acute myocardial infarctions may have SGOT titers greater than 400 units.

4. In patients with myocardial infarctions, titers above 650 units should lead one to suspect that functional hepatocellular injury, on a congestive basis, is concomitantly present.

5. Whereas high transaminase levels in myocardial infarctions not accompanied by liver congestion have no short term prognostic value, high SGOT titers in myocardial infarctions associated with acute hepatic congestion presage poorly for the patient and shock is more likely to complicate the clinical course.

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SUMMARIO IN INTERLINGUA

Acute Congestion Hepatic Como Factor In Elevar Le Titros De Transaminase Glutamic Oxaloacetic Del Sero A Supra 400 Unitates

Un analyse de titros de transaminase glutamic oxaloacetic del sero (TGOS) de plus que 400 unitates resultava in le sequente conclusiones:

1. Acute congestion hepatic pote causar elevate titros de TGOS. Quando le congestion es sever, alte titros de plus que 500 unitates pote resultar. In casos in que le congestion es satis sever pro causar necrosis hepatic, titros de usque a 3000 unitates pote occurrer.

2. Le importantia del "factor de congestion hepatic" in alte titros de TGOS (supra 400 unitates) es sublineate per le significative differentia inter le titro medie in non-complicate infarcimento myocardial (482) e le titro medie in omne casos de acute congestion hepatic (1042), sin reguardo al etiologia.

3. Il occurre non infrequentemente que acute infarcimento myocardial es associate con un titro de TGOS de plus que 400 unitates.

4. In patientes con infarcimento myocardial, le constatation de titros de plus que 650 unitates deberea suggerer le suspicion del presentia concomitante de un compromisso functional del cellulas hepatic, a base de congestion.

5. Durante que alte titros de transaminase in casos de infarcimento myocardial sin concomitante congestion hepatic ha nulle importantia pro le prognose a curte vista, alte tal titros in casos de infarcimento myocardial associate con acute congestion hepatic constitue un mal augurio pro le patiente, e le probabilitate de un complication del curso clinic per le occurrentia de choc es correspondentemente plus grande.

INFECTIOUS MONONUCLEOSIS

AN ANALYSIS OF 100 CASES WITH PARTICULAR ATTENTION TO DIAGNOSIS, LIVER FUNCTION TESTS AND TREATMENT OF SELECTED CASES WITH PREDNISONE

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Infectious mononucleosis is a regular invader of college campuses and military installations because the disease, for some unknown reason, seems to have a predilection for young people of college and military age. It apparently has no seasonal, sex, or geographic preference. It is an acute disease, usually benign and self-limited, but occasionally associated with disturbing or serious complications.

In 1889, Pfeiffer[61] described in children an acute illness which he called "glandular fever." The term "infectious mononucleosis" was introduced in 1920 by Sprunt and Evans[77] when they described a small group of cases with fever, lymph node enlargement and abnormal lymphocytes in the blood. Although the term "infectious mononucleosis" has been widely adopted, the general assumption has prevailed that this disease and "glandular fever" are the same. However, Sprunt and Evans evidently did not think so, nor did Downey and McKinlay[23] who, in 1923, made an excellent and classical description of the atypical lymphocytes of infectious mononucleosis. Glandular fever, said Downey and McKinlay, occurs in children and infrequently presents a significant pharyngitis, whereas infectious mononucleosis occurs in adults and pharyngitis is a prominent symptom.

In 1932, Paul and Bunnell[59] reported a heterophile sheep cell agglutination that occurs in infectious mononucleosis and in serum sickness. Since then the heterophile test has assumed a position of major importance as a diagnostic test. In 1935, Davidsohn and Walker[18] developed a technique of absorption tests using guinea pig kidney and beef erythrocytes to distinguish infectious mononucleosis from serum disease.

Since the introduction of the term infectious mononucleosis in 1920 there has been accumulated a voluminous literature on the disease. No attempt will be made here to present a review of this literature, and reference will be made only to certain representative articles that recount such experiences and opinions as may be pertinent to this discussion.

Despite the efforts of many capable researchers, the etiology of infectious mononucleosis remains unknown, and a controversy regarding its diagnosis continues, as it has since 1920. The common clinical manifestations of fever, pharyngitis, lymphadenopathy, enlargement of the spleen, and in more recent years evidence of hepatic dysfunction are well known; the changes

in the circulating lymphocytes are readily acknowledged; the heterophile agglutination test is widely accepted as a diagnostic pillar (Bernstein[10], Davidsohn, Stern and Kashiwagi[17], Hoagland[33], Liebowitz[51] and Tidy[82]); yet there is no general agreement among physicians as to what should constitute the minimum diagnostic criteria for the disease. This has led to some confusion as to what should be called infectious mononucleosis and what should not. The disease has frequently been described as protean, having many widely different symptoms and characteristics (Bernstein[10], Editorial[24], Halcrow, Owen and Rodger[32], Mitchell and Zetzel[55], Tidy[82]). It has been described as having a low index of contagiousness, shown by its failure to spread through dormitories and institutions (Hoagland[35]). It is commonly treated on open wards without evidence of dissemination (Contratto[13]). Yet there are reports of epidemics, in Army camps and schools (Bernstein[10], Halcrow, Owen and Rodger[32], Tidy[82], Wechsler, Rosenblum and Sills[85]). This is a distinct paradox.

In our efforts to learn more about this disease we have tried to correlate our observations in cases seen at a college health center during the past 7 years. An analysis of 100 such cases represents the basis of this report.

SELECTION OF CASES. The selection of cases for study involves again the question of diagnosis. In the literature on infectious mononucleosis one often finds the diagnostic criteria loosely stated to be: the characteristic clinical findings, the presence of atypical lymphocytes, and a positive heterophile test. These may not be further qualified. Frequently any 2 of the 3 factors are accepted as diagnostically sufficient (Bennett *et al.*[8], Halcrow, Owen and Rodger[32], Kaufman[44], Press, Shlevin and Rosen[62], Rapaport[65], Schultz and Hall[72]). It is obvious that various different diseases are at times described as cases of infectious mononucleosis (Hoagland[35], Shubert, Collee and Smith[74]). This is perhaps better than the reverse situation, however, in which too strict criteria of diagnosis would exclude many cases that should be so designated.

THE HETEROPHILE AGGLUTINATION TEST. To some the heterophile test is the *sine qua non* of diagnosis (Hoagland[34], Kilham and Steigman[47], Liebowitz[50]); others attach to it a lesser significance (Editorial[25], Goldman, Fishkin and Peterson[31], Keiper[46], Press, Shlevin and Rosen[62]). All in all, for reasons to be suggested shortly, the reliability of this test as it is commonly performed has probably been somewhat over-rated.

There is abundant evidence to suggest that the heterophile test without absorption studies is nonspecific (Davidsohn, Stern and Kashiwagi[17], Goldman, Fishkin and Peterson[31], Liebowitz[49], Schultz[73]). When combined with a characteristic pattern of absorptions, the test has been claimed to be specific (Davidsohn, Stern and Kashiwagi[17], Hoagland[34], Liebowitz[50]). Possibly it is when it is positive, but it does not follow that a characteristically positive test is always attainable. In fact, there is good reason to believe that seronegative cases do occur (Dempster[20], Erf[27], Evans[29], Gardner and Paul[30], Goldman, Fishkin and Peterson[31], Liebowitz[52], Peterson[60]). Also the vagaries of the test itself, its temporal variations (the reaction being sometimes transient, sometimes delayed), variations in technique and in the sheep cells employed, all weaken the reliability of the test as the sole foundation upon which the diagnosis should rest (Editorial[25], Erf[27], Goldman, Fishkin and

Peterson[31], Stuart *et al.*[80]). That this is generally conceded by most authors is shown by the fact that few reported series of cases will claim a positive heterophile test, even without absorptions, for every case in the series. We have received reports of "strongly positive" and "negative" from tests made in different laboratories on the same sample of serum.

Extensive serological studies by Zarafonetis and his coworkers[86,87,88,89] have suggested that many of the inconsistencies encountered in the heterophile test are not inherent in the principle of sheep cell agglutination by infectious mononucleosis antibodies but are the result of several variables in laboratory techniques commonly employed in the test. The more important variables involve the concentration of sheep cells, the presence in some sera of cold hemagglutinins for sheep cells, variability of the reaction of erythrocytes from different sheep, and the loss of agglutinability of sheep cells that have been preserved in storage.

Some human sera possess cold agglutinins which on refrigeration produce agglutination of the cells from susceptible sheep, causing thereby false-positive heterophilic agglutination (Stuart *et al.*[80], Zarafonetis *et al.*[88,89]). Such agglutinations may reach titers of 1:128, 1:256, possibly even higher (Zarafonetis, Oster and Colville[88]). The cold agglutinin effect may easily be avoided or removed by simply reading the heterophile test after incubation at 37° C. or by rewarming the serum-cell mixture after overnight refrigeration (Stuart *et al.*[80], Zarafonetis, Oster and Colville[88]). Zarafonetis and Colville[89] have shown that such cold agglutinins act as Forssman antibodies and that titers after rewarming compare favorably with those after guinea pig absorption.

The evidence that cells from different sheep vary in their capacity to react to the heterophile antigen (Keiper[46], Zarafonetis and Oster[87]) and the evidence that sheep cells after storage may lose their capacity to react (Keiper[46], Zarafonetis and Oster[87]) are undoubtedly important in explaining some of the negative serological tests encountered in patients who otherwise present clinical and hematologic findings characteristic of infectious mononucleosis.

By controlling these variable factors, Zarafonetis and his associates[86,87,88,89] apparently have been able to eliminate most of the false positive and false negative heterophile reactions, which presumably account for much of the discrepancy and confusion found in the clinical application of this test.

Still further lack of agreement prevails in regard to the interpretation of the heterophile test; that is the question, what constitutes a positive test? In the absence of absorptions, levels acceptable to different authors vary all the way from titers of 1:56 (Hoagland[34], Kaufman[44], Schultz and Hall[72]) to 1:1792 (Liebowitz[51]). After guinea pig absorption some say the titer should not drop more than three tubes or to no less than ⅛ of the nonabsorbed titer (Davidsohn, Stern and Kashiwagi[17]); others may accept levels of any degree after guinea pig absorption (Evans[29]).

There is no doubt that absorption tests are of definite value and that they may increase the reliability of the heterophile test, but they are not infallible. Sometimes they fail to show a clear-cut pattern that is capable of accurate interpretation (Goldman, Fishkin and Peterson[31], Press, Shlevin and Rosen[62]).

Zarafonetis states that there can be no arbitrary division between normal heterophile titers and those diagnostic of infectious mononucleosis[86,87]. He be-

lieves that serologic diagnosis depends upon the demonstration of a dynamic antibody response, indicated by the rise and fall of titers in a series of heterophile tests in which samples of all of the sera in the series are tested simultaneously with the same batch of sheep cells[86,87].

In our laboratory an agglutination titer of 1:112 without absorptions has proved to be the most useful minimum to be considered a positive heterophile test. The serum-cell test mixtures are never refrigerated, but are incubated at room temperature for at least 2 hours. When absorption studies are made, we consider the test positive if the titer after guinea pig absorption does not fall to less than ¼ of the original titer and if the titer after beef cell absorption falls significantly below this level, usually to zero or nearly so.

ATYPICAL LYMPHOCYTES. The significance of the hematologic changes in infectious mononucleosis has, like the heterophile test, been the subject of disagreement. Lymphocytosis and atypical lymphocytes are recognized as the usual hematologic manifestations of this disease (Downey and McKinlay[23], Liebowitz[51], Limarzi, Paul and Poncher[53]). The characteristic alteration of the lymphocytes we consider highly important in diagnosis and often more useful than the heterophile test. It has been repeatedly emphasized, however, that both of these phenomena are nonspecific (Bender[6], Liebowitz[51], Litwins and Liebowitz[54], Randolph and Gibson[64]). Lymphocytosis is common in a variety of disturbances. Likewise atypical lymphocytes have been reported in various conditions, among them several known virus diseases: measles, infectious hepatitis, herpes, atypical pneumonia, and others. They have been reported also in bacterial infections, and in malignant lymphoma, leukemia, anemia, allergies, and even in supposedly normal persons. Too little attention has been given, however, to the quantitative relationship of the lymphocytes, normal and atypical, to the other leukocytes (Stevens, Bayrd and Heck[79]). These quantitative factors we believe to be important. A few authors have drawn attention to the fact that although atypical lymphocytes may be present in small numbers in a variety of diseases, they do not generally exceed 10% of the total leukocyte count except in infectious mononucleosis (Bakst and Liebowitz[4], Bender[5], Denber and Liebowitz[21], Litwins and Liebowitz[54]).

We consider the blood picture of infectious mononucleosis to be characteristic when 50% or more of the total leukocytes are lymphocytes and when 15% or more of the total leukocytes are atypical lymphocytes.

In most of our patients 60% or more of the total white blood cells were represented by lymphocytes and 20% or more of the total leukocytes were atypical lymphocytes (Table 1). Often the lymphocytes were as high as 70% or 80% and occasionally above 90%. Atypical lymphocytes often reached levels of 40% to 50% and extended in one case as high as 85%.

TABLE 1.—DIFFERENTIAL LEUKOCYTE COUNTS

Lymphocytes:	
50%	in 94% of cases
60%	in 81% of cases
70%	in 53% of cases
80%	in 19% of cases
90%	in 3% of cases
Atypical Lymphocytes:	
10%	in 95% of cases
15%	in 93% of cases
20%	in 78% of cases
30%	in 52% of cases
50%	in 16% of cases

We have found atypical lymphocytes at times in blood samples from patients with various other diseases but usually these cells are few. We have seen them more frequently and in higher numbers in measles than in other diseases except mononucleosis. An examination of the records of 41 cases of rubella showed that atypical lymphocytes were present in 8 cases. In 14 cases of rubeola atypical lymphocytes were noted in 6. In 2 of these cases the abnormal cells were briefly as high as 15% but the corresponding total lymphocytes were only 38% and 32%. In one case the total lymphocyte percentage was 50 but the corresponding atypical lymphocytes were less than 15. In all the other cases the total lymphocytes and atypical cell percentages were both small.

In the beginning a patient with infectious mononucleosis may have a completely normal white count and differential. But the blood smear may change very significantly within as short a period as 24 hours, showing an increase in lymphocytes and the presence of atypical cells. Continued reexamination of the blood may then show an increasing lymphocytosis with a progressive rise in atypical lymphocytes. In the case of fever of undetermined origin, or that of posterior cervical adenopathy or of exudative pharyngitis in which the possibility of infectious mononucleosis is entertained, it is important to repeat the blood smear every day or two. Such efforts may be rewarded by a sudden increase in lymphocytes and the appearance of atypical lymphocytes, which may rapidly increase to such levels as to be diagnostically significant.

DIAGNOSTIC CRITERIA FOR CASES IN THIS SERIES. Although the diagnosis should be based upon the clinical picture, the hematologic findings and the heterophile test, we are unable to draw sharp or absolute limits and we think the diagnosis should be relative, with all 3 factors being considered together. We believe, however, that some quantitative dimensions are necessary as a basis for classification, realizing that in the absence of a known etiology for this disease our limits must necessarily be arbitrary. None the less we have found them practically useful in our own attempts at diagnosis, prognosis and management (Tables 2 and 3).

TABLE 2.—CRITERIA FOR DEFINITIVE DIAGNOSIS

1. Clinical findings
   - Post. cervical lymphadenopathy
   - Pharyngitis
   - Palpable spleen
   - Fever

Plus

2. Characteristic blood picture
   50% or more lymphocytes and
   15% atypical lymphocytes

Plus

3. Positive heterophile test
   Titer 1:112 or higher. Lower titer permissible with typical absorption pattern.

TABLE 3.—CRITERIA FOR PRESUMPTIVE DIAGNOSIS

1. Compatible clinical findings

plus

2. Characterstic blood picture

or

Positive heterophile test

With compatible clinical findings, a characteristic blood picture (50% lymphocytes and 15% atypical lymphocytes), and a positive heterophile test (1:112), we think a definite diagnosis of infectious mononucleosis is justified. Eighty-three per cent of our cases satisfied these criteria.

If the blood is not characteristic, but if the heterophile test is positive and the clinical findings are compatible, we

think a presumptive diagnosis can be made. Similarly, if the blood and clinical findings are characteristic but the heterophile test is still not positive, we consider the diagnosis presumptive. Repeated tests eventually will provide, in many instances, the data needed for definite diagnosis. Sometimes the heterophile response is considerably delayed and the patient may be nearly well by the time it becomes evident. On the other hand, the blood picture may regress ahead of the heterophile reaction, and if a patient is seen for the first time late in his illness, the heterophile reaction may be characteristically positive but typical blood counts may never be observed. In such cases absorption tests may be helpful in confirming the probability of the diagnosis in retrospect. Absorption tests are also of particular value when they may help to determine the significance of an inadequate or borderline heterophile titer (Liebowitz[51], Paul[58], Press, Shlevin and Rosen[62]).

Because the data were incomplete in one respect or the other, 17% of our cases are placed in the presumptive diagnosis category (Table 4).

TABLE 4.—RESULTS OF DIAGNOSTIC TESTS IN 100 CASES OF INFECTIOUS MONONUCLEOSIS

Heterophile test positive in	91%
Absorption tests (guinea pig kidney and beef erythrocytes)	47%
Circulating leukocyte pattern typical in	92%
Definite diagnosis	83%
Presumptive diagnosis	17%

FALSE POSITIVE SEROLOGY. Transient false positive serological tests for syphilis, unrelated to the heterophile titers, have been reported in infectious mononucleosis (Bernstein[10], Kaufman[43], Kolmer, Ginsburg and Lynch[48], Paul[58]). Although no such false positive reactions were recorded in our series, too few tests were performed to be statistically significant.

CLINICAL MANIFESTATIONS. Clinically our cases have shown moderate variation in severity, but usually they have had an acute febrile illness lasting 1 to 3 weeks after the onset of fever, and all have made a complete recovery. It may be observed from the table (Table 5) that lymphadenopathy, pharyngitis, fever and splenomegaly represented the most common clinical signs and symptoms of our series. Some of the symptoms represented are those that might be expected to occur in any febrile disease.

TABLE 5.—CLINICAL MANIFESTATIONS IN 100 CASES OF INFECTIOUS MONONUCLEOSIS

Sign or Symptom		*% Cases*
Lymphadenopathy		95
Cervical alone	55	
Nodes in addition to cervical	40	
Pharyngitis		91
With exudate	49	
Splenomegaly		51
Fever (temperature 100°–105°)		79
Malaise		76
Headache		55
G.I. symptoms		47
Anorexia	26	
Nausea and vomiting	17	
Diarrhea	8	
Cough		31
Abdominal pain		14
Petechiae of palate		13
Rash		12
Pain in eyes		10
Hepatomegaly		6
Edema of uvula		6
Edema of upper eyelids		5
Meningismus		3
Pneumonitis		3

The most constant clinical manifestation was cervical lymphadenopathy. It was present in 95 cases. The posterior group of cervical nodes was chiefly

affected but anterior nodes were often simultaneously involved, and occasionally were principally involved. Axillary adenopathy occurred not infrequently, but definite inguinal adenopathy was uncommon. Whenever the axillary or inguinal lymph nodes were involved, the cervical nodes were simultaneously affected. Contratto[13] has made the same observation. Adenopathy confined to the cervical nodes was common.

Pharyngitis was present in 91 cases. In several cases it was very severe, associated with edema, pain, and difficulty of swallowing. In many cases "sore throat" was the chief complaint and the worst symptom from the patient's point of view. Exudate was present in half the cases with pharyngitis. At times it was extensive, being a thick, dirty-white membrane which, however, could be removed rather easily and without bleeding. Superficial, aphthous-like ulcerations were sometimes seen on the soft palate or anterior tonsillar pillars. Twenty-seven cases of exudative pharyngitis had throat cultures. Beta streptococci were found in 8 of these.

Such physical signs as edema of the upper eyelids, edema of the uvula, and palatal petechiae to which attention has been called by Bender[6], Hoagland[33] and others were not frequent in our series.

Seventy-nine cases had fever (temperature elevations varying from 100° to 105°). The average duration of the febrile period was 4 days, with a span of 1 to 14 days.

Of 84 cases in which the limits of the illness could be determined with reasonable accuracy, the total duration of illness varied from 6 to 48 days, with an average of 17.6 days. This represents the total period from the onset of symptoms until the patient was both subjectively and objectively well.

LABORATORY FINDINGS. In 91 cases the heterophile test was considered positive. In 80 cases the titer was 1:224 or higher. In 47 cases absorption tests were done. All were positive. Of those patients who did not have absorption studies, 14 showed a progressive rise in heterophile titer from negative to positive levels.

In 77 cases in which the information was considered reliable, the first heterophile test performed varied from the second to the twentieth day of the illness, the average being the seventh day of illness. The average day on which the test was first positive was the ninth day of illness, with a span of 2 to 22 days. The first heterophile test performed was positive in 70% of the cases.

The average day of illness on which the blood differential count was first made was the fifth day. The average day it became typically positive was the seventh day. Therefore the blood picture became positive on the average some 2 days before the heterophile test. However, suggestive changes in the lymphocytes often were observed 2 or more days earlier still. These early blood changes frequently were responsible for prompting the initial heterophile test.

The characteristic blood picture was present at some time in a total of 92 cases. The highest lymphocyte percentage recorded was 94% and the highest percentage of atypical lymphocytes was 85%.

Both lymphocytosis and atypical lymphocytes developed more or less simultaneously and there was no significant difference in the time required for each to reach our selected critical levels.

A number of articles in recent years have stressed the importance of liver function disturbance as expressed by liver function tests (DeMarsh and

Alt[19], Editorial[26], Evans[28], Hoagland and McCluskey[37], Houck[38], Jordan and Albright[40], Peterson[60], Schultz and Hall[72], Sullivan *et al.*[81]). Pathologic studies at necropsy and after liver biopsy have verified the existence of an hepatitis in a large majority of the cases (Allen and Kellner[2], Hoagland and McCluskey[37], Sullivan *et al.*[81], Wadsworth and Keil[84], Ziegler[90]). This has led many authors to conclude that hepatitis is a natural and integral part of the disease infectious mononucleosis, and many have begun to consider the disease not so benign as it was for many years thought to be (Davidsohn[16], Houck[38], Nelson and Darragh[56]). Distinct differences of opinion are expressed in the literature as regards the nature and the severity of the hepatitis. Some authors after a study of necropsy and biopsy material have reached the conclusion that the hepatitis is quite similar to and at times indistinguishable from that of infectious hepatitis (Custer and Smith[15], Kass and Robbins[42], Reichman, Burke and Davis[70], Wadsworth and Keil[84]). Others, however, on the basis of similar studies maintain that the hepatitis of these 2 diseases is different (Hoagland and McCluskey[37], Nelson and Darragh[56], Sullivan *et al.*[81]). Their studies suggest that although an actual hepatitis is present, there is less liver cell destruction, less disturbance of hepatic architecture and little tendency to fibrous tissue proliferation and distortion. Such variable concepts have led to different attitudes toward the management of patients, especially in regard to the length of hospitalization and the restriction of activity after the acute symptoms have subsided (DeMarsh and Alt[19], Hoagland and McCluskey[37], Liebowitz[51], Rapaport[65], Schultz and Hall[72]).

We performed 198 liver function tests on 62 of our patients (Table 6). On the basis of our experience we would agree that some alteration of liver function seems to be characteristic. However, from a clinical standpoint we believe that there is a difference between the hepatitis of an average case of infectious mononucleosis and that of an average case of infectious hepatitis. Rarely in our series was the liver enlarged or tender. Anorexia and other gastrointestinal symptoms were not severe nor prolonged.

TABLE 6.—RESULTS OF LIVER FUNCTION TESTS

	Tests	*Cases*	*Positive Cases*	*% Positive Cases*
B S P	87	54	43	80
Ceph. floc.	53	32	23	75
Thymol turb.	34	28	5	18
Serum bilirubin	14	14	3	21
Icterus index	10	10	0	
Total	198	62		

Contrary to the reports of some other investigators (Bennett *et al.*[8], Davidsohn[16], Jordan and Albright[40], Rubin[71], Schultz and Hall[72]), the thymol turbidity test was not often increased. Nelson and Darragh[56] report somewhat similar experience with this test. The bromsulphthalein or BSP test[10], however, was commonly positive. It generally became positive relatively early, usually about the beginning of the second week, or about the time the heterophile became positive. Then it tended to revert to normal fairly promptly, that is within 7 to 10 days. The cephalin flocculation test (Evans[28]), on the other hand, usually became positive later than the BSP and had a tendency to persist for a longer time, even 2 to 3 months. We found the BSP test helpful in judging the time when the patient should be allowed to become ambulatory.

Eighty-seven BSP tests were performed on 54 patients. In 43 cases one or more positive tests were obtained, an incidence of 80%. Fifty-three cephalin flocculation tests were done on 32 patients, 23 of whom or 75% had one or more positive tests. It may be worthwhile to note that only 9 of the 53 cephalin flocculation tests were classified as 4+ or strongly positive. The majority of positive tests were graded 3+.

Thirty-four thymol turbidity tests were performed in 28 cases, only 5 of whom had a positive test. This is an incidence of 18% and represents a sharp contrast from the BSP and cephalin flocculation tests. None of the thymol tests was strongly positive.

Jaundice is reported with variable frequency in infectious mononucleosis. Some authors report the symptom in as many as 10% (Abrams[1], Bennett *et al.*[8], Paterson and Pinniger[57], Schultz and Hall[72]) to 20% (Kilham and Steigman[47], Rapaport[65]) of their patients. Liebowitz[51] reported jaundice in 28% of one series. Others report either no jaundice or a rare case (Davidsohn[16], DeMarsh and Alt[19]). The average reported incidence is about 5% (Liebowitz[51]). None of the patients in our series was jaundiced. Serum bilirubin tests were done in 14 cases, and of these 3 showed a slight elevation to 1 to 2 mg. per 100 ml.

THERAPY. The treatment of infectious mononucleosis has always been symptomatic and supportive. There is no specific therapy. Numerous antibiotics have been tried and their effects have been reported occasionally with some hopeful enthusiasm (Kaufman[45]), but the general consensus sooner or later has been that they have no specific effect in this illness. During the last 3 or 4 years there have been several reports of favorable effects from the use of adrenal corticosteroids (Bender and Houghton[7], Bernard, Mathé and Sigal[9], Brutsche and Naegele[12], Cronk and Naumann[14], Doran and Weisberger[22], Johnson[39], Redmond[69]).

We have tried this type of therapy in a few selected cases. Altogether we have treated 17 patients with oral prednisone with rather encouraging results. The hormone did not obscure the valuable laboratory signs, namely, the blood smear, the liver function tests and the heterophile test. We had no complications that we could attribute to the steroid.

Each steroid treated case was given antibiotics as a prophylactic measure against secondary bacterial invasion. The steroids were administered orally, in comparatively small doses, and for rather short periods of time. Prednisone (Meticorten), the preparation used, was given in dosage of 20 mg. daily for 1 to 3 days and then tapered off by the reduction of 5 mg. on each succeeding day.

Most of the patients who received prednisone were those who had rather intense symptoms, such as severe pharyngitis with much edema and difficulty in swallowing, or a pronounced febrile reaction. Almost uniformly these patients were subjectively improved within 24 hours. Objective improvement, especially the subsiding of edema and exudate of the pharynx and decrease in the size of cervical nodes, was observed within 2 or 3 days.

We believe that steroid therapy deserves further trial. It is not certain that such therapy will be advisable routinely in infectious mononucleosis. The course of the illness is self-limited and in some patients it is mild. It remains to be shown that steroid therapy will have any effect in reducing the duration of the illness or that it will be effective in the prevention of complications. In our small group of Meticorten treated cases the total dur-

ation of the illness was substantially the same (18 days) as that of the larger group that received no steroids.

The majority of our patients were treated symptomatically and with bed rest, followed by a period of restricted activity. All patients were given a general diet. We did not think that the liver alteration required special dietary measures or lipotropic drugs. Although patients not infrequently had mild anorexia, they were usually able to eat reasonably well, and parenteral fluids were unnecessary. When the blood showed a marked drop in the number of granulocytes, we gave broad spectrum antibiotics prophylactically to guard against secondary infection.

Patients were kept at bed rest when they had fever, agranulocytosis of high degree, BSP retention or hepatic enlargement, or both, and when the spleen was large and tender. When these signs had disappeared and the patients began to feel well, they were allowed to be ambulatory. Their activities were restricted, however, when the spleen was still enlarged but not tender, when malaise and fatigue were prominent, when agranulocytosis was moderate, or when they showed evidence of vasomotor instability.

On this regimen all of our patients recovered completely within a period of 1 to 2 months. Repeated physical and laboratory follow-ups were made in most cases. We had no cases of definite relapse. One patient who left school and went home for convalescence was said to have had subsequently an attack of atypical pneumonia from which he recovered within a short period. Whether or not this could have been infectious mononucleosis pneumonitis or a coincidental unrelated pneumonitis we do not know.

Most of our patients were able to resume their university studies within 2 or 3 weeks, and none had symptoms of prolonged duration. Hoagland has reported similar experience with his patients who were West Point Cadets or soldiers at Fort Benning[37]. We agree with him that the resumption of physical activity when the patient is afebrile, feels and appears well is probably not hazardous to the liver. The cephalin flocculation test may remain positive in some degree for a period of 2 or 3 months, even if all other signs of the disease have disappeared and the patient feels well. Repeated follow-up tests show a gradual return to normal. It is doubtful if any significant activity restriction is essential because of the slower regression of the cephalin flocculation test (Sullivan *et al.*[81]).

From our experience we assume that recurrence of infectious mononucleosis is rare. This is similar to the experience of others (Bernstein[10], Contratto[13], Paterson and Pinniger[57]). None of our patients had proven recurrences. Now and then we have encountered a history of previous infectious mononucleosis in patients with the disease, but we have not obtained satisfactorily documented evidence of the accuracy of the earlier diagnosis.

COMPLICATIONS. A rather wide variety of complications has been reported in infectious mononucleosis, although such complications are comparatively unusual (Bernstein and Wolff[11], Contratto[13], Davidsohn[16], Hoagland[34], Smith[76]). Perhaps the most dangerous and startling is that of rupture of the spleen (Hoagland and Henson[36], Smith and Custer[75]). Fortunately this accident does not occur often, but when it does, it presents a surgical emergency. It is important, therefore, to be on guard for such a catastrophe, which is said to be most likely to occur during the third week of illness (Hoagland and Henson[36], Houck[38], Smith and Custer[75]), and therefore when the patient is usually well on the way to

recovery. As a precautionary measure it is wise to restrict more carefully the physical activities of patients who have significant enlargement of the spleen. Frequent or vigorous palpation should be avoided (Smith[76]).

Various neurological disturbances have been reported from time to time as complications of infectious mononucleosis: meningitis, encephalitis, peripheral neuritis, myelitis, optic neuritis, and Guillain-Barré syndrome (Bernstein and Wolff[11], Raftery *et al.*[63], Ream and Hessing[68], Smith[76], Tidy[82]). Acute psychosis has been recorded as a complication (Raymond and Williams[66]).

Among the other complications myocarditis, pericarditis, and pneumonitis have been reported (Houck[38], Schultz and Hall[72], Smith[76], Stevens, Bayrd and Heck[78]). Purpura hemorrhagica has been reported several times (Angle and Alt[3], Jorgenson[41], Volpe, Sparks and Mautner[83]). There are reports of anemia, both hemolytic and nonhemolytic (Read and Helwig[67], Schultz and Hall[72]). Various acute abdominal symptoms have been ascribed to the presence of enlarged mesenteric lymph nodes (Smith[76], Stevens, Bayrd and Heck[78]).

A variety of dermal reactions have been reported, with an incidence of 1 to 25% (Bernstein[10], Contratto[13], Kilham and Steigman[47], Smith[76], Tidy[82]). Skin rash occurred in 12% of our cases. There is nothing particularly characteristic about the rash except that it is generally mild and transitory. It may at times be confused with German measles.

Jaundice properly may be considered a complication because it does not commonly occur.

If we consider abnormal liver function tests as a usual part of the clinical picture of infectious mononucleosis, we had only 16 complications in our series of patients. None had jaundice, 12 had skin rash, and one patient had thrombocytopenic purpura, with platelets dropping to a level of 25,000. Three patients had pneumonitis, one during the acute illness and 2 during the late convalescent period. We encountered no definite neurological complication and no splenic rupture.

It is the complications of infectious mononucleosis, which are unusual and infrequent, that have given the disease the reputation of being protean and unpredictable. The fact that the symptoms of the complication sometimes may precede the usual clinical and laboratory manifestations of the primary disease has contributed further to this concept. However, we have found these usual clinical and laboratory manifestations to be reasonably consistent. Our experience would lead us to support the contention of Hoagland, that infectious mononucleosis is not really a protean disease[34,36].

Summary. The diagnosis of infectious mononucleosis has been a controversial subject for more than 35 years. The differences of opinion have involved principally the significance and the interpretation of both the hematologic changes and the sheep cell agglutination or heterophile antibody test. Secondary, in most instances, to such variable opinions, a diversity of clinical manifestations has been described. These discrepancies are discussed and emphasis given to the concept that accuracy of diagnosis is a relative matter, dependent upon no single feature of the disease but upon the inter-relationship of various diagnostic factors, clinical and laboratory. Practical diagnostic criteria are suggested.

An analysis is made of 100 cases with respect to clinical data, diagnosis, treatment, duration of illness, and complications. The analysis indicates a reason-

able consistency of clinical and laboratory findings among these cases.

The divergent reports of investigators regarding alterations of the liver are discussed. Evidence is presented to suggest: (1) that alterations of liver function are quite common, and (2) that the usual hepatitis of infectious mononucleosis is probably different from that generally to be found in infectious and serum hepatitis.

Treatment is generally symptomatic and supportive, and prolonged bed rest is usually unnecessary. A small, selected group of 17 patients was treated with oral prednisone, which appeared to initiate prompt symptomatic improvement, especially the lessening of pharyngitis. The hormone did not obscure the valuable laboratory signs, but also it did not appear to shorten the total duration of illness. The ultimate value of steroid therapy in this disease remains to be proven.

It is the complications of infectious mononucleosis which, together with insufficient discrimination in the diagnosis, have given the disease the reputation of being protean.

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(Interlingua on page 506)

PHENYLBUTAZONE THERAPY IN PATIENTS WITH RHEUMATIC DISEASE AND COINCIDENTAL ESSENTIAL HYPERTENSION

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A SIGNIFICANT number of patients seen in arthritis clinics have coincidental essential hypertension. They are primarily elderly individuals who are being treated for osteoarthritis, the rheumatic disease most frequent in an older age group where hypertension is also more common. Phenylbutazone (Butazolidin) is one of the few effective drugs in the treatment of osteoarthritis (Denko, Ruml and Berquistal[2], Kidd, Boyce and Freyberg[3], Kuzell *et al.*[4], Steinbrocker *et al.*[5]). When hypertension is present, the benefits afforded by phenylbutazone are frequently denied because of fear of the consequences of sodium retention (Brodie *et al.*[1], Wilkinson and Brown[6], William[7]) which occurs with this medication, thus eliminating one of the better drugs for therapy.

This study was conducted in order to determine to what extent phenylbutazone can be successfully employed in these individuals. In addition, patients with other rheumatic diseases who appeared at our Arthritis Clinic having coincidental essential hypertension are included. Fifty-four patients were studied, 43 with osteoarthritis, 6 rheumatoid arthritis, 3 chronic bursitis, 1 fibrositis, and 1 disseminated lupus erythematosus.

Methods. Patients were observed under conditions common for office and clinic care of the ambulant patient. Each subject was examined weekly during the first few weeks. Intervals between visits were then lengthened in accordance with the individual clinical status. Blood pressures were determined at each visit after the patient had been relaxed in a sitting position and conversing with the physician for from 5 to 10 minutes.

Improvement in the rheumatic disease was recorded in per cent as a composite estimate of relief from pain and stiffness, increased range of motion, and, where applicable, change in the degree of synovitis.

Phenylbutazone* was initially administered in doses of 200 mg. 3 times daily after meals except in those individuals adjudged to be in functional cardiac Class III or IV (New York Heart Association Criteria†) where the

*Geigy Pharmaceuticals supplied the phenylbutazone for this study.

†Classification of Functional Capacity was based upon that presented in "Nomenclature and Criteria for Diagnoses of Disease of the Heart and Blood Vessels" published by the New York Heart Association, New York, 1953.

Class I: No limitation of physical activity due to heart disease.
Class II: Comfortable at rest. Slight limitation of physical activity.
Class III: Comfortable at rest. Marked limitation of physical activity.
Class IV: Unable to carry on any physical activity without discomfort.

dose was 100 mg. 4 times daily. This was continued for 5 to 7 consecutive days and, infrequently, for 14 days. If no improvement resulted, the drug was stopped without further trial. If relief was obtained, the medication was likewise discontinued only to be resumed when symptoms recurred. The drug was then administered at the same or smaller dosage level until a satisfactory response returned, and then discontinued again. This intermittent method of drug administration was followed throughout the study. One half of the patients were treated for 2 weeks or less, and the balance over longer periods of time up to 2 years.

Examination at each visit included a careful search for evidence of toxicity, such as blood dyscrasias, renal, gastrointestinal, skin, and cardiac changes. Body weight and evidence of edema were recorded. Blood counts and urinalyses were performed at regular intervals, usually once every 2 weeks for the first month of therapy, and less often later.

Restriction of salt in the cooking of food and at the table was advised in the more severe hypertensive cases and in those of functional cardiac Class III or IV.

Average age of the patients was 66 years, 96% of whom were in the age group above 50 (Fig. 1).

The degree of hypertension is noted in Fig. 2. Systolic levels of 200 or more mm. Hg were present in 16 cases, diastolic levels of 100 or more in 29 patients.

The cardiac classification was I in 67% of patients; 20% were in functional Class II, and the balance (6 cases) fell in Class III or IV.

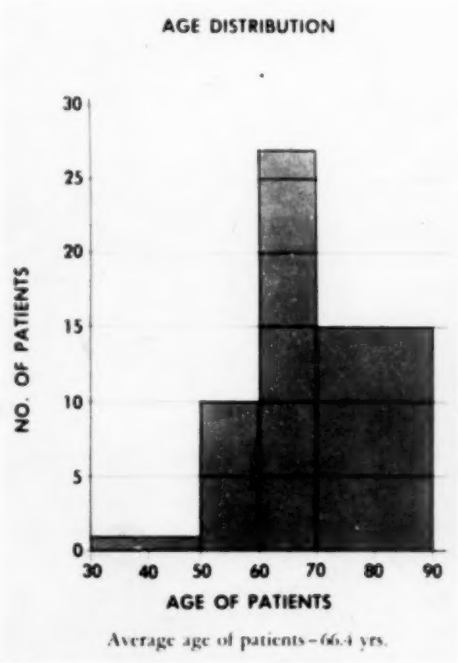

Fig. 1

Results. Ten individuals showed an increase in systolic blood pressure of 10 mm. Hg or higher during therapy with phenylbutazone. Eighteen had a fall in systolic blood pressure of 10 mm. Hg or more (Fig. 3). The greatest elevation in systolic pressure was 50 mm. Hg in one patient on therapy for 2 weeks whose blood pressure rose temporarily from 142/96 to

192/98. Otherwise, systolic elevations above 20 mm. Hg did not occur. Diastolic pressures were similarly altered in most of these patients, but to a lesser degree; in only one instance did it rise as much as 20 mm. Hg. All other elevations in diastolic pressure were below 10 mm. Hg.

Seven of the 10 patients with an increase in systolic blood pressure were simultaneously observed to have gained weight greater than one pound, but 9 of 18 with a fall in pressure likewise gained weight. No changes in cardiac status were apparent in any subject save for one patient whose congestive failure improved without explanation.

A satisfactory therapeutic response (greater than 50% improvement) in relief of rheumatic symptoms was obtained in 2/3 of cases (Fig. 4).

The total of untoward physiologic or toxic effects noted were: ankle edema, 6 cases; gastrointestinal distress, 4 cases; and 2 each of leukopenia and pruritus. In 4 instances (7.6%) reactions were considered sufficiently severe to require discontinuing medication. These consisted of: 1 patient with edema (salt intake was not restricted); 1 with pruritus; 1 with gastrointestinal complaints; and 1 with a fall in white count, but without signs of agranulocytic angina. In no instance was the elevation of blood pressure of such a degree as to warrant discontinuing therapy.

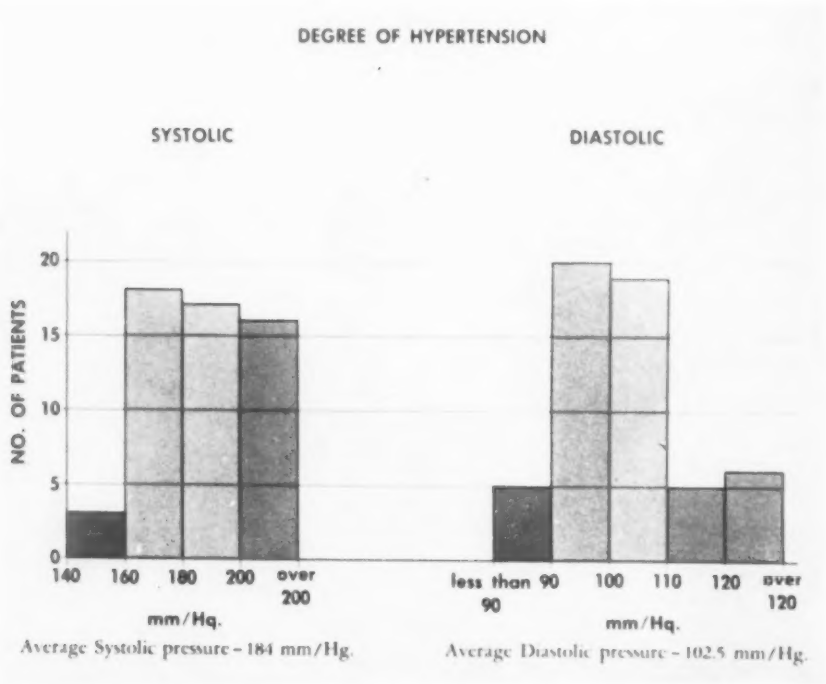

Fig. 2

Discussion. The blood pressures recorded during therapy with phenylbutazone were not significantly altered. The variations noted were probably the result of the method of examination

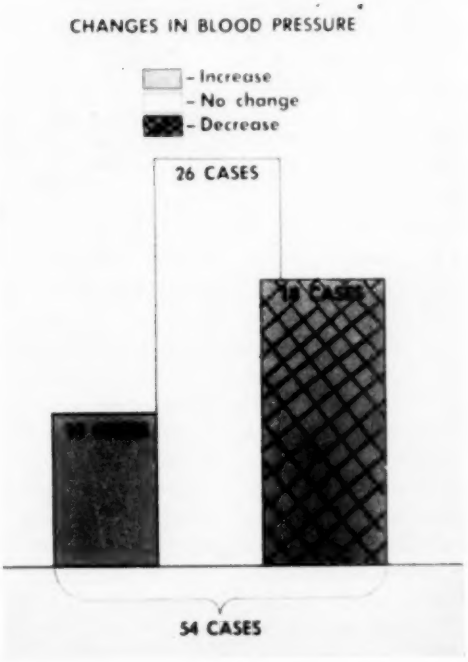
CHANGES IN BLOOD PRESSURE
- Increase
- No change
- Decrease
26 CASES
54 CASES

Fig. 3

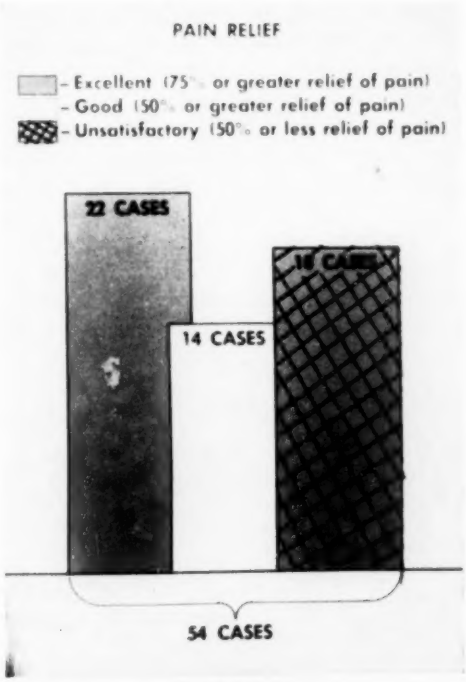
PAIN RELIEF
- Excellent (75% or greater relief of pain)
- Good (50% or greater relief of pain)
- Unsatisfactory (50% or less relief of pain)
22 CASES
14 CASES
54 CASES

Fig. 4

which was considered more practical from the standpoint of the practitioner who would probably proceed in a similar fashion. Increases in blood pressure which did occur were not sustained and were not clinically important. In those individuals with blood pressure elevations during therapy and who simultaneously gained weight, correlation with sodium retention might be considered. However, half the patients with a decrease in pressure also gained weight suggesting no probable relationship between the two. If blood pressure rise was secondary to sodium retention, salt restriction might control this factor.

The intermittent method of administration of phenylbutazone was undertaken in an effort to decrease the incidence of toxic reactions. Since no permanent antirheumatic effect of this drug had previously been noted in most patients with varying rheumatic diseases, it was not felt necessary to recommend its continuous daily administration in the absence of symptoms. It was not possible to determine if the incidence of undesirable reactions was lessened in this small series of patients. Toxicity occurred in 14 cases (26%), but was severe enough to require discontinuing medication in only 4 instances.

The absence of ill effects from phenylbutazone therapy on the blood pressure or cardiac status indicates that the compound may be successfully administered to the type of patient in this study. But, it should be emphasized that most of these hypertensive individuals did not have associated severe congestive heart failure as only 6 patients were in functional cardiac Class III or IV. Conclusive statements regarding the use of phenylbutazone in all patients with arthritis and coincidental essential hypertension, therefore, cannot be formulated. Frank contraindication of the drug or severely restricting its use in uncomplicated hypertensive rheumatic disease patients seems unwarranted.

Summary. 1. Fifty-four patients with various rheumatic diseases and coincidental essential hypertension were treated with phenylbutazone intermittently for periods up to 2 years.

2. Satisfactory relief of rheumatic symptoms was obtained in two-thirds of the patients.

3. Blood pressure was not significantly increased and in no instance was severe enough to require discontinuing therapy.

4. No apparent change in cardiac status resulting from phenylbutazone therapy was observed.

5. Toxic reactions requiring withdrawal of phenylbutazone therapy occurred in 4 of 54 patients.

6. Patients with rheumatic disease and coincidental uncomplicated hypertension can be treated with phenylbutazone without special regard to blood pressure.

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SUMMARIO IN INTERLINGUA

Therapia A Phenylbutazona In Patientes Con Morbo Rheumatic E Coincidente Hypertension Essential

1. Cinquanta-quatro patientes con varie morbos rheumatic e coincidente hypertension essential esseva tractate con phenylbutazona in cursos intermittente durante periodos total de usque a 2 annos.

2. Grados satisfacente de alleviamento del symptomas rheumatic esseva obtenite in duo tertios del patientes.

3. Le resultante augmento del pression de sanguine non esseva significative. In nulle caso esseva illo satis grave pro requirer le interruption del therapia.

4. Esseva notate nulle apparente alteration del stato cardiac in consequentia del therapia a phenylbutazona.

5. Reactiones toxic requiriente abstention ab phenylbutazona occurreva in 4 del 54 patientes.

6. Patientes con morbo rheumatic e coincidente hypertension non-complicate pote esser tractate con phenylbutazona sin respecto special al pression de sanguine.

DIABETIC NEUROPATHY PRECIPITATING AFTER INSTITUTION OF DIABETIC CONTROL

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The pathogenetic background for the development of diabetic neuropathy has been tacitly assumed to be a result of poor diabetic control over a prolonged period of time. For example, Joslin[9] states "true diabetic neuritis in almost, if not all instances, follows a period of uncontrolled diabetes." Duncan[3] wrote "peripheral neuritis in diabetes is a common complication of grossly neglected diabetes, neglected over long periods." Rundles[12] categorically states that "onset of diabetic neuropathy is always during uncontrolled diabetes." Similar views have been expressed by other authorities in this field (Bonkalo[1], Goodman *et al.*[7], Martin[10]).

This conclusion has recently been challenged, at least in a specific group of patients in whom the neuropathy presented as the initial clinical manifestation of diabetes (Ellenberg[4], Sullivan[15]). The clinical picture in these patients was unaccompanied by any signs or symptoms of uncontrolled glycosuria. This observation had been previously recorded, usually as an incidental finding in a survey of a large number of patients with diabetic neuropathy.

The present paper will present, through documented case reports, another deviation from the "poor control" concept of etiology. In these cases, neuropathy was paradoxically precipitated or severely exacerbated following the institution of good control and while the patients remained under good control.

Case Reports. CASE 1. This 59-year-old man entered the Mount Sinai Hospital complaining of severe pain in both lower extremities. One year ago he noted moderate progressive weight loss, accompanied by polyuria, polydipsia and polyphagia. Four months ago a diagnosis of diabetes mellitus was made. He was placed on a dietary regimen without insulin. His symptoms improved, but not completely. Two months later, therefore, he was given 15 units of protamine zinc insulin daily. Several days later the patient experienced for the first time, sharp burning pain and paresthesias over the anterior aspect of both thighs. The pains continued in great severity to the time of admission. They were characterized as lancinating and knife-like, increased during the night and on lying down, and relieved by moderate exercise. More recently, he noted progressive weakness and atrophy of the right thigh muscles. The patient denies any back pain or back trauma, and no pain on coughing, sneezing or motion. In addition, the patient has noted depression and associated anorexia, so that there has been weight loss in spite of recent good diabetic control. The past history is essentially noncontributory. The family history is significant in that his father and a sister have diabetes.

Physical examination revealed a well developed, moderately well nourished man. Pupils were normal, fundi did not reveal any diabetic retinopathy; no nodes were palpable; heart and lungs were normal; blood pressure 140/95; liver palpable 1 finger breadth below the right costal margin; all peripheral pulses were present. Neurological examination revealed the cranial nerves to be normal; the knee jerks and ankle jerks were absent bilaterally and the biceps and triceps reflexes were markedly diminished. There was definite atrophy of the right thigh with marked weakness of this extremity. There was some diminution of vibratory sensation, more marked in the right lower extremity than the left.

Laboratory examination showed: hemoglobin 14.6 gm.%; white blood cell coun

9,000, with normal differential; sedimentation rate 10 mm. per hour; urinalysis normal; blood glucose 170 mg. per 100 ml.; blood urea nitrogen 12 mg. per 100 ml.; total protein 7.1 gm.% with normal albumin and globulin ratio; calcium, phosphorus, bilirubin, acid and alkaline phosphatase values were all normal. Liver function studies were normal. Blood Wassermann test was normal. Lumbar puncture revealed clear fluid under normal pressure; there were no cells; the total spinal fluid protein was elevated to 120 mg. per 100 ml. Roentgenographic examination of the chest, lumbosacral spine, long bones and intravenous pyelogram were all normal. Pantopaque myelography was within the limits of normal.

COMMENT. The acute precipitation of the neuropathy followed shortly after the institution of control by diet therapy and insulin. This was preceded by 2 months of moderate, though incomplete dietary regulation. There were no other demonstrable factors that could be implicated. The clinical syndrome, including nocturnal exacerbation of pain relieved by walking, the neurological findings, the depression with its associated anorexia, and the elevated cerebrospinal fluid protein, is characteristic of diabetic neuropathy.

CASE 2. This 63-year-old colored man entered the hospital complaining of burning of the lower extremities, pruritus and weakness. Ten years ago a diagnosis of diabetes mellitus was made following the onset of polydypsia and polyuria. Since then, control has been maintained through the intermittent use of insulin on a self-regulatory basis. Until the present illness, he was able to engage in heavy manual labor and there was no weight loss. Ten months ago he developed an episode of anterior chest pain, associated with some dyspnea. At this time he was told by his doctor that he must lose weight. The diagnosis at that time is unknown. He was given several injections and started on a highly restricted low-caloric, low-carbohydrate diet. As a consequence thereof, he lost 35 pounds in the next month. About a month after starting the diet, he was given protamine zinc insulin 20 units every morning, which was increased to 40 units. Approximately 2 months after starting control with diet (8 months ago) and while under excellent control, he developed weakness of the right lower extremity, which progressed so that he was conscious of dragging the right foot. Six months ago he developed pruritus over most of the body. Five months ago there was added to this a severe burning sensation, most marked over the lower abdomen and anterior thighs. The last is now his chief complaint. This symptom is markedly increased at night; pajamas and even bed linens are described as causing excruciating discomfort. In conjunction with this, he has been depressed. In addition to the 35 pounds he had lost during the first month of his severe diet, he lost 10 more pounds after control was achieved because of moderate anorexia.

General physical examination was essentially unremarkable except for evidence of weight loss and his obvious discomfort. The heart did not appear to be enlarged, the rhythm was regular, there were no murmurs, blood pressure 150/90; lungs were clear; the liver was palpable one finger breadth below the costal margin. The chief abnormalities were confined to the neurological examination and consisted of miotic pupils, the right greater than the left, both reacting poorly to light; funduscopic examination revealed evidence of diabetic retinopathy. There was marked generalized muscular wasting, including the thenar and hypothenar eminences and the interosseus muscles of the hands. The left upper extremity was weaker than the right. The knee jerks were present but both ankle jerks were absent. Weakness of the right lower extremity was present with slapping gait of the right foot. Vibratory sensation was defective in both feet and both thighs. During the course of the examination, it was noted that the patient had marked perspiration over the lower abdomen as well as the upper thighs.

Laboratory investigation showed normal hemoglobin, red cell count and white cell count; the urine revealed a trace of albumin, occasional clumps of white blood cells; blood urea nitrogen, total protein, albumin-globulin ratio, bilirubin, cholesterol, alkaline and acid phosphatase, cephalin flocculation, thymol turbidity and uric acid were all normal. The blood sugar was elevated to 208 mg. per 100 ml. 2 hours after eating. Gastric analysis revealed the presence of free hydrochloric acid. Twenty-four hour urine for porphyrins was negative. Electroencephalogram was normal. Electrocardiogram showed changes indicative of some myocardial involvement. A biopsy of the sural nerve was reported as showing patchy nerve degeneration predominately affecting the myelin sheath. This

was considered compatible with, but not diagnostic of diabetic neuropathy. Lumbar puncture on two occasions revealed clear colorless fluid, no cells, no evidence of block and a total protein elevation to 78 and 91 mg. per 100 ml. Wassermann tests of serum and of the spinal fluid were both negative. Pantopaque myelogram revealed no abnormalities.

Sympathetic blocks with xylocaine were essentially unsuccessful, but there was transitory improvement following the intravenous administration of procaine.

COMMENT. This patient had had diabetes mellitus over a 10-year period. Although not under formal regulatory control, he managed successfully to continue work at very heavy labor and maintain his weight. Some 10 months ago an undiagnosed episode led to a serious attempt at control via marked dietary regulation resulting in a rapid weight loss of 35 pounds in one month. At this point insulin was added but weight loss continued in the face of adequate control. Then, while under excellent control, there appeared a severe incapacitating radiculoneuropathy with marked autonomic component. The sequence of events would seem to clearly implicate the control induced by the harsh diet, and then further supplemented by insulin.

CASE 3. This 60-year-old white man developed constant pain in both lower extremities 11 months before admission. The pain radiated down the anterior surfaces of both thighs and legs, more marked on the left than the right. It was not related to exertion, not relieved by heat, and worse at night. Eight months later he developed the classical syndrome of diabetes mellitus characterized by polyuria, polydipsia, nocturia, weight loss of fourteen pounds, hyperglycemia, glycosuria and severe pruritus of both legs. He was started on therapy consisting of diet and protamine zinc insulin, 24 units every morning. The pruritus disappeared, but the pain became acutely exacerbated, so much so that large amounts of opiates. none of which had been necessary hitherto, had to be given, especially at night. Progressive weakness of the lower extremities accompanied the increased pain to the point of his being almost invalided. Past history was not contributory except that he had a depressive episode in the past. The present symptoms were accompanied by marked depression. There was no family history of diabetes.

Examination revealed a well developed and well nourished man. Blood pressure was 154/96. There were a few hemorrhages and exudates in the right fundus; the liver was palpable at the costal margin; all peripheral pulses were readily palpable; there was evidence of excoriation of the anterior aspects of both legs. Neurological examination revealed advanced weakness of both thighs, more marked on the left than on the right, and involving the quadriceps more than the hamstrings; weakness of the left hip flexors; absence of both knee jerks; ankle jerks were present; and loss of vibratory perception in the left lower extremity.

Laboratory investigation revealed: urine specific gravity 1.008, albumin two plus, glycosuria one plus, 12 red blood cells and 1 to 2 white blood cells per hpf; hemoglobin 14.4 gm.%; red blood count 4.5 million per c.mm.; white blood count 6,900 per c.mm. with normal differential; blood Wassermann test was negative; blood urea nitrogen 14 mg.; bilirubin 0.2 mg.; calcium 10.1 mg.; phosphorus 3.4 mg. per 100 ml.; alkaline phosphatase 6 King-Armstrong units; blood sugar 140 mg. per 100 ml. Lumbar puncture yielded clear, colorless fluid with no evidence of block, colloidal gold negative, cell count zero and total protein elevated to 63 mg. per 100 ml.

COURSE. The glycosuria and hyperglycemia which had been brought under control with the use of insulin and diet, presented no problem. However, the symptoms and weakness which had become so exaggerated continued to increase. Simultaneously, the depression became more marked and, although his diabetes was under excellent control, there was persistent weight loss as a result of the associated anorexia. This continued for 3 months. During this period of time many other diagnoses were considered in view of the unresponsiveness of the condition and relative paucity of sensory findings. However, after the 3 months, the patient began to improve, and the recovery proceeded at a remarkably rapid rate, so that 2 months later, he was essentially back to normal. Follow-up 5 years later indicates that the patient remained well with no recurrence of these symptoms.

COMMENT. This patient exemplifies the acute aggravation of the nerve in-

volvement following the institution of good diabetic control. The symptoms continued to increase even while under good control for 3 months. They then regressed and eventually disappeared, although the patient continued to take insulin. He has been on insulin ever since with no recurrence. Of added interest in this case is the onset of symptoms of uncontrolled glycosuria 8 months following the onset of the neurological complaints, which were the initiating clinical manifestations of the diabetes.

CASE 4. This 57-year-old white woman entered the hospital complaining of progressive weakness in the lower extremities. Diabetes mellitus was diagnosed 5 years ago following the onset of polydypsia and polyuria. This had been controlled with diet alone until 6 months ago when the symptoms increased and the patient also developed pruritus vulvae. Therapy with tolbutamide was started; it was discontinued in 3 weeks because of lack of therapeutic effect. She was then given isophane insulin, 40 units daily, which served to bring the diabetes under excellent control. At this time she began to complain of a sensation of pins and needles in the lower extremities. Approximately one month after insulin was started, she noticed weakness in both lower extremities. This increased progressively, so that she developed difficulty in walking, easy fatiguability, difficulty in arising from a chair and climbing stairs. Not long after, she became unsteady and fell on several occasions when her knees gave way. The paresthesias in her legs and feet also increased, but to a lesser degree. Along with these symptoms, she manifested a significant depression and marked anxiety. Past history included radiation therapy to the ovaries 12 years ago for menorrhagia. Family history was negative except for the presence of diabetes in several of her cousins.

The general physical examination was not remarkable. There were no enlarged nodes or thyroid enlargement; the heart was not enlarged, the rhythm was regular and there were no murmurs; the liver was not palpable; pelvic examination was negative; the peripheral pulses were palpable. The neurological examination showed the cranial nerves to be entirely normal; there was no diabetic retinopathy. The abnormal findings were confined to the lower extremities. Here there was distinct and marked weakness of both hips with difficulty in getting out of a chair, there was marked weakness of flexion at the knees; the thigh and calf muscles were severely atrophied bilaterally; knee jerks and ankle jerks were absent but no pathological reflexes were obtained; vibratory sense was impaired below both iliac crests, and there was some loss of position sense of the toes.

Laboratory examination included: hemoglobin 13.2 gm.%; blood count was entirely normal; urinalysis was negative; blood urea nitrogen, calcium, phosphorus, total protein, cholesterol, alkaline phosphatase and carbon-dioxide combining power were all normal; gastric analysis showed the presence of free hydrochloric acid. Roentgenographic examination of the chest and of the spine were normal; absorption of radioactive iodine was normal; spinal fluid was clear, contained no cells, the total protein was elevated to 102 mg. per 100 ml., collodial gold was negative, and the manometric determinations were normal. Blood and spinal fluid Wassermann tests were negative; electrocardiogram and electroencephalogram were normal.

COURSE. Shortly after admission, and while insulin administration was continued, the patient began to improve spontaneously. This continued to progress rapidly to resolution.

COMMENT. The sequence of events in this instance indicates that the severe and incapacitating neuropathy occurred only after control of the diabebtes had been obtained. The clearing of symptoms in the face of continued use of insulin would seem to absolve the latter from any direct part in this process.

Discussion. The precipitation or exacerbation of diabetic neuropathy following the institution of control of the diabetes has been previously recorded (Jordan[8], Rudy and Epstein[14]). Originally the etiologic agent in this category of patient was suspected to be insulin, the hormone acting as a toxic agent. In fact, this syndrome has been referred to in the literature as "insulin neuritis." The only recorded instance wherein insulin actually seemed to act in this fashion is the report of Caravati[2]. His patient developed a purely sub-

jective neuropathy 4 weeks after starting treatment with insulin. The symptoms disappeared 3 days after stopping the drug. Sudden clearing of this sort is entirely incompatible with diabetic neuropthy. Re-institution of insulin therapy again produced the same subjective symptoms. Skin testing with four different brands of insulin resulted in 3 positive and one negative reaction. Further therapy with the nonreacting brand was uneventful. This apparently is a case of idiosyncrasy to some of the accompanying impurities (proteins) rather than the insulin *per se*.

The neuropathy following insulin control has also been attributed to hypoglycemia by Goodman *et al.*[7]. In their group of patients, the symptoms were mild and transitory, there were no objective findings and all complaints promptly disappeared on restoration of normoglycemia. Their cases obviously did have transitory hypoglycemic manifestations but this clinical picture is entirely unrelated to diabetic neuropathy and hence has no bearing on the present issue. It should be noted, nevertheless, that there is an entity of hypoglycemic neuropathy (Mulder, Bastron and Lambert[11]). It is characterized primarily by atrophy of muscle groups and occurs in the course of long-standing, severe, recurrent hypoglycemic attacks, such as is found in adenoma of the pancreatic islets. Hypoglycemia of this degree, frequency and duration is not present in our type of case; further, the neurological picture is different and inconsistent with diabetic neuropathy.

Against this type of neuropathy being a result of insulin toxicity or sensitivity are the facts that the symptoms, signs, spinal fluid findings and course are identical with all other forms of diabetic neuropathy. Further, clearing of the syndrome while therapy with insulin is continued militates strongly against this being a drug-induced condition.

Perhaps the crux of the argument is the fact that diabetic neuropathy may be precipitated by any factor that will control the hyperglycemia and glycosuria. Thus, control by diet alone and without insulin has resulted in the same sequence of events and the same clinical picture and course (Rudy[13], Case III). More recently, control with the oral hypoglycemic agent, tolbutamide, has also been observed to precipitate or accentuate diabetic neuropathy (Ellenberg[6]). Hence, the term "insulin neuritis" is a misnomer; the insulin is not the noxious agent but acts merely as the medium for control of the diabetes which in turn, in certain instances, leads to neuropathy.

Along with so many other factors in diabetic neuropathy, the etiology in general remains obscure (Ellenberg[5]), and in this specific group is unknown. A possible explanation may lie in the relatively sudden change of the homeostasis, thus producing the equivalent of a stress phenomenon. Some weight should be given this thought inasmuch as many stress situations, including coma, surgery, infection and trauma, have been known to immediately precede the onset of neuropathy in the diabetic patient. It is hoped that investigation along these lines may shed some light on this obscure matter.

Summary. Contrary to the generally accepted dictum that diabetic neuropathy occurs only during uncontrolled diabetes, clinical case reports are presented illustrating the onset or acute exacerbation of diabetic neuropathy following the institution of control of the hyperglycemia and glycosuria with insulin and diet. Although insulin has been suspected as being the toxic etiologic agent under these circumstances, several factors seem to clearly

absolve it of this role. These include: 1) the neuropathy following the institution of insulin control of the diabetes is identical with all other forms of diabetic neuropathy as regards symptoms, signs, spinal fluid findings, and course; 2) the neurologic picture tends to improve and even disappear despite the continued use of insulin; 3) control of the diabetes by measures other than insulin may also lead to the precipitation of neuropathy. Thus, insulin is not the noxious agent but acts as the medium for control of the diabetes which, in certain instances, leads to neuropathy.

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SUMMARIO IN INTERLINGUA

Neuropathia Diabetic, Precipitate Post Effectuation De Un Stato Regulate Del Diabete

In nonconformitate con le generalmente acceptate judicamento que neuropathia diabetic occurre solmente in diabete non-regulate, reportos clinic es hic presentate de casos que illustra le declaration o le exacerbation acute de neuropathia diabetic post le effectuation de un stato regulate del hyperglycemia e del glycosuria per medio de insulina e mesuras dietari. Ben que le suspicion ha essite exprimite que insulina es le agente etiologic toxic sub iste circumstantias, plure factores pare clarmente absolver lo de iste responsabilitate. Iste factores include le sequente: (1) Le neuropathia occurrente post le effectuation de un stato regulate del diabete per medio de insulina es identic con omne altere formas de neuropathia diabetic in le symptomas, le signos, le constatationes in le fluido spinal, e in le curso. (2) Le syndrome neurologic tende a meliorar se e mesmo a disparer in despecto del continuate uso de insulina. (3) Le regulation de diabete per mesuras altere que le administration de insulina es etiam capace a precipitar un neuropathia. Assi insulina non es le agente noxie sed age como medie pro le effectuation de un stato regulate del diabete le qual, in certe casos, produce effectos neuropathologic.

PAPER ELECTROPHORETIC STUDIES OF POSTMORTEM SERUM PROTEINS

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The role of the serum globulins, particularly gamma globulin in immune mechanisms, makes the measurement of these substances of considerable interest in various disease states. Some diseases, especially those due to infection, end in death after fulminate courses that afford little chance for study in the living state. If reliable determinations of the serum globulins could be obtained from postmortem sera, some light might be shed on the immune mechanisms in these situations.

A survey of the literature on the electrophoretic examination of postmortem sera revealed a paucity of studies in this field. Schleyer[2] made electrophoretic examinations of serial serum specimens from a number of cadavers and concluded that the study yielded little data of medicolegal value. Spain, Bradess and Greenblatt[3] examined the sera postmortem in several premature infants and reported that in cases of sudden death, the gamma globulin was depressed.

Methods and Materials. The material presented in this paper comprises the electrophoretic studies of 15 sera obtained 4 to 48 hours after death from patients dying of a number of diseases.

Blood was drawn at necropsy directly from the heart or aorta and allowed to stand until clotted. The clotted blood was centrifuged and the separated serum stored at 5° C. until examined (serum stored at this temperature for several months showed no change in the electrophoretic pattern). Fifteen usable sera were obtained from 155 necropsies. The low useful yield resulted from the frequent incidence of hemolysis in the specimens and from the occurrence of gross intravascular clotting which precluded aspiration of the blood.

An attempt was made to obtain both pre- and postmortem specimens in the case of critically ill and moribund patients. For one or the other of the reasons cited above, plus the occasional failure to obtain permission for necropsy, this attempt succeeded in only one instance. The method employed for the electrophoretic analysis was described by Davis[1].

The percentage distribution of the electrophoretic fractions of the various sera and the time after death until the collection of the specimens are given in Table 1. The diagnosis in each case is given only for interest and to illustrate the wide range of clinical conditions from which the material was drawn. Normal values with their standard deviations were obtained from the sera of 49 staff and student members of the U.S. Naval Medical School.

Discussion. The sole object of this study was to determine if and for how long serum proteins retained their identities postmortem. The postmortem patterns were found to conform closely enough to the normal to warrant the conclusion that the patterns of sera from the living are not grossly different from those of the dead, within the first 36 hours postmortem. Of particular interest are the findings that the gamma globulin is readily recognized

and that there is a fairly consistent elevation of the beta globulin in postmortem serum. The latter finding was also noted by Schleyer in 2 cases. The observation that gamma globulin is readily recognized in the serum after death suggests that search for it in sudden death might reveal cases of hypogammaglobulinemia not recognized in life. The elevated beta globulin may be an interesting postmortem change or may reflect agonal changes in the sera of seriously diseased patients. Continued studies of sera from cases of sudden traumatic death should establish the time of the beta globulin increase.

Summary. A study was made of the electrophoretic characteristics of serum obtained at necropsy. It was found that the usual serum proteins were readily identifiable and that an increase in the beta globulin was a fairly constant finding. It would appear from the data that the electrophoretic examination of postmortem serum is a use-

TABLE 1

Patient	*Hours Post-Death*	*Percentage Distribution*					*Diagnosis*
		Albumin	*Alpha-1*	*Alpha-2*	*Beta*	*Gamma*	
Normal		52.9±2.0	6.4±1.5	10.5±2.4	12.8±2.2	16.6±2.8	
A	34	34.8	6.6	19.2	19.0	20.4	Myocardial infarction
B	13	40.5	15.8	9.5	20.9	13.3	Leukemia
C	Within 48 hours	41.5	6.6	11.6	17.0	23.8	Pulmonary edema
D	Within 48 hours	49.8	6.0	9.8	22.0	12.6	Intracranial hemorrhage
E	14 hrs. old	57.3	7.3	9.0	8.8	18.0	Intra-uterine death
F	24	24.8	7.2	13.0	21.2	33.8	Lobar pneumonia
G	8	45.3	5.3	12.8	18.0	18.7	Acute myocardial infarction
H	6	26.9	9.7	16.6	17.3	29.5	Bronchogenic carcinoma
I	48	35.7	11.2	24.4	18.0	10.7	Carcinoma of esophagus
J	13	33.1	11.8	15.8	19.3	19.5	Malignant melanoma
K	23	38.6	8.7	7.9	20.9	24.0	Periportal cirrhosis
L	4 days pre-death	49.2	8.2	12.3	14.8	15.5	
	Within 48 hours	34.4	9.4	13.3	27.0	11.7	Arteriolonephrosclerosis
M	13	33.6	9.4	15.9	26.4	14.7	Congestive heart failure
N	6	42.4	8.7	15.2	14.1	19.6	Carcinoma of pancreas
O	4	27.4	8.9	14.6	23.2	25.9	Multiple injuries

ful investigative procedure and that it may be of value in cases of sudden death where hypogammaglobulinemia is suspected.

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SUMMARIO IN INTERLINGUA

Studios A Electrophorese A Papiro De Proteinas De Sero Post Morte

Esseva effectuate un studio del characteristicas electrophoretic de sero obtenite al necropsia. Esseva trovate que le usual proteinas seral esseva facilemente identificabile. Augmentos de globulina beta esseva un constatation satis constante. Le datos pare indicar que le examine post morte de sero es un utile technica de investigation. Illo es possibilemente de valor in casos de morte subitanee in que le presentia de hypogammaglobulinemia es suspicite.

IMMUNOTHROMBOCYTOPENIA INDUCED BY NOVOBIOCIN

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Novobiocin is a drug which has antibacterial activity against Gram-positive and certain Gram-negative microorganisms. This drug has found its widest application in the treatment of resistant staphylococcal infections. It has been shown to have a high incidence of toxic effects, the most frequent of which have been skin eruptions, fever, and diarrhea (Bridges, Berendes and Good[5], Welch *et al.*[17]). Hematologic disorders, such as leukopenia and eosinophilia, resulting from the use of novobiocin have also been described (David and Burgner[7], Finland and Nichols[9], Martin *et al.*[13], Simon and Rogers[14]). To our knowledge, thrombocytopenia has not been previously reported. A patient, having developed thrombocytopenic purpura under novobiocin therapy, afforded us the opportunity to investigate the pathogenesis of this disorder.

Case Report. M.B. (Ohio State University Hospital #608490), a 28-year-old white woman, was admitted to the orthopedic service for the second time on February 26, 1958. Since 2 years of age she has had osteomyelitis and draining sinus tracts on her feet. A diagnosis of syringomyelia was made in her early adolescence. Her feet have required multiple surgical procedures, including bilateral partial amputations. She was first seen in the orthopedic outpatient clinic in August, 1957, at which time roentgenographic examinations revealed a chronic osteomyelitis of the left foot. Local conservative measures were ineffective and the patient was admitted for the first time in December, 1957, with an acute cellulitis of the left foot stump. She received penicillin (400,000 units) and streptomycin (0.5 gm.) twice daily for 6 days. She became afebrile after 2 days of therapy and remained so thereafter. She was discharged after 10 days and was followed as an outpatient in the orthopedic clinic for approximately 2 months. No further antibiotic or chemotherapy was given. The patient was then readmitted for an elective orthopedic procedure to remove the infected bone and to attempt closure of the draining sinus tracts.

On admission the patient was febrile (101.4° F.). Physical examination revealed 2 draining sinuses on the ventral surface and a warm erythema of the dorsum of the left foot. The distal thirds of both feet were surgically absent. Loss of pain and temperature sensations of both lower extremities were noted.

The leukocyte count on admission was 7,200 cells per c.mm., with a differential count of 62% neutrophils, 33% lymphocytes, and 5% eosinophils, and with adequate platelets present on the blood smear. Her hemoglobin and hematocrit were 9.2 gm. per 100 ml. and 33%, respectively. A culture of material from the sinus tract drainage failed to show any pathogenic organisms.

The patient was started on novobiocin (0.5 gm.) every 6 hours. She became afebrile after one day and felt well. On the fourth hospital day she received 500 ml. of whole blood to correct an anemia which was thought to be the result of chronic infection.

At 11:00 a.m. on the eighth hospital day she first noted a very slight diffuse mottling of her skin. At noon she received 0.5 gm. of novobiocin after which the drug was discontinued. One hour later a pruritic macular rash developed. At 3:00 p.m. petechiae were noted for the first time. Within an hour a generalized purpura had developed (Fig.

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1). The rash became maculopapular and the splenic tip became palpable. Her temperature rose to 101° F. A platelet count revealed 34,000 platelets per c.mm., the Lee-White coagulation time was 10.5 minutes, and the prothrombin time was within normal limits. After a hematology consultation was obtained, the patient was transferred to the hematology service.

Fig. 1.—This photograph demonstrates the patient's purpuric eruption which developed 8 days after the beginning of novobiocin therapy.

An examination of her bone marrow revealed increased numbers of megakaryocytes and mild erythroid hyperplasia. Platelet counts performed by the indirect method of Dameshek revealed no platelets. The patient was started on prednisone and Benadryl (0.01 gm. and 0.1 gm., respectively, every 6 hours). She was given ACTH (25 units every 12 hours) by slow intravenous drip for 3 days. ACTH was then given intramuscularly at a dosage of 15 units daily for 4 days. On the day following the start of hormonal therapy the patient became afebrile. Her spleen was no longer palpable. No further purpuric lesions were noted and the platelet count rose steadily from 0 to 72,000, to 132,000 to 410,000 platelets per c.mm. on successive days. With the exception of the complaint of severe pruritis, the patient felt well throughout the course of purpura. Following recovery from the initial episode of purpura, a test dose of 0.5 gm. of novobiocin was given with the patient's consent. Several *in vivo* and *in vitro* tests were performed to determine the pathogenesis of this thrombocytopenia.

Experimental Methods and Materials. 1. GENERAL. All syringes and other glassware used in these experiments were silicone-coated except where the procedures required glass-contact. Sodium citrate (3.8%) adjusted

to pH 7.48 was used as the anticoagulant. The standard 2 syringe technique was used to collect all blood samples.

Novobiocin was made up to final concentrations of 0.05 gm. per 100 ml. and 0.25 gm. per 100 ml. No difference in the effect of these novobiocin concentrations upon platelet function was noted.

Platelets and platelet-rich plasmas were obtained from healthy blood group O donors. Platelet suspensions were washed 4 times with physiological saline and adjusted to contain about 300,000 platelets per c.mm. after dilution with physiological saline.

2. PLATELET COUNTS. Platelet counts were determined by the indirect method of Dameshek[6]. Two separate samples were obtained and the results were accepted only if they agreed within 5%. All platelet counts were done by the same individual in order to minimize errors in individual performance.

3. PLATELET AGGLUTINATION. Platelet agglutination tests were performed as outlined by Stefanini and co-workers[16] and later modified by the same authors[15]. Controls using the patient's serum and plasma obtained before the administration of the test dose of this drug were treated similarly. The samples obtained at this time will be referred to henceforth as *drug-insensitive plasma or drug-insensitive serum*. Samples obtained after the administration of the test dose of novobiocin will be referred to as *drug-sensitive plasma or drug-sensitive serum*. Normal control plasma or normal control serum was obtained from 3 healthy individuals. In this way the patient served as her own control in those instances in which serum or plasma were used in the agglutination tests. Agglutination tests were observed with a phase contrast microscope at a magnification of 400×.

4. PROTHROMBIN UTILIZATION. Prothrombin utilization was studied by means of the prothrombin consumption test as modified by Dreskin[8]. Tests of inhibition of normal prothrombin consumption were performed by addition of 0.1 ml. of novobiocin solution and 0.1 ml. of the patient's prothrombin-free serum to 2.0 ml. of whole blood prior to clotting. Physiological saline solution served as a control for the serum and the novobiocin solution when this drug was added to the test samples.

5. CLOT RETRACTION. Clot retraction was estimated as outlined by Barkham and Tocantins[3]. The effect of inhibition of clot retraction by the test serum was shown by the addition of 0.1 ml. of the patient's serum and 0.1 ml. of novobiocin to 1.0 ml. of normal blood. Three hours after clotting at 37° C. the serum was poured off and its volume measured. All tests were performed in duplicate. *Drug-insensitive serum* served as an additional control to the normal serum.

6. THROMBOPLASTIN GENERATION. The thromboplastin generation test was performed using the method of Biggs and Douglas[4]. The *final platelet suspension* was made up to one-third of the original plasma volume such that the concentration of platelets in the *drug-sensitive plasma* was approximately 150,000 platelets per c.mm. The term *adjusted final platelet suspension* refers to a suspension prepared from the patient's *drug-sensitive plasma* containing approximately 800,000 platelets per c.mm.

7. ACCELERATION OF OPTICAL CLEARING OF PLATELET-RICH PLASMA. The effect of adding the patient's serum to normal platelet-rich plasma was observed microscopically using the method of Stefanini and Dameshek[15]. One-half milliliter of deprothrombized serum from the patient and from the controls was placed in 1.5 ml. of normal platelet-rich plasma and allowed to incubate at room temperature for 3 hours. The degree of clearing of the platelet suspension was observed visually.

8. PATCH TESTS. Patch tests were performed by the method of Freedman, Brady and Barr[10], in which pastes of novobiocin sodium and saline solution or propylene glycol on a small gauze pad were applied to the patient's skin. Patches were kept in place for 24 to 48 hours. Negative pressure was applied to the skin under the patch for 5 minutes.

Results. 1. THE EFFECTS OF ORALLY ADMINISTERED NOVOBIOCIN UPON THE PLATELET COUNT. Within 8 hours after the administration of the test dose of the drug, the platelet level had decreased to a value less than one-half of that of the pre-drug level, reaching a nadir in 12 hours and slowly rising again to pre-drug levels during the next 96 hours (Fig. 2).

2. THE DEMONSTRATION OF PLATELET AGGLUTININS AND LYSINS. Platelet agglutination and lysis were demonstrated in experiments in which the drug solution, *drug-sensitive plasma or drug-sensitive serum* and normal platelets were combined. All controls, including those in which *drug-insensitive serum* or *drug-insensitive plasma* was used,

failed to show agglutination or lysis. The addition of novobiocin solution to normal platelet suspension also failed to produce agglutination or lysis, even after incubation at 37° C. for 10 minutes.

3. INHIBITION OF CLOT RETRACTION. Samples to which *drug-sensitive serum* or *drug-sensitive blood* was added (Table 1) showed inhibition of clot retraction. Controls with saline and *drug-insensitive serum* or *drug-insensitive blood* showed normal retraction.

4. ACCELERATION OF OPTICAL CLEARING. Mixtures of platelet-rich plasma and *drug-sensitive serum* showed marked clearing of turbidity after incubation at room temperature for 3 hours. Mixtures of platelet-rich plasma and control or *drug-insensitive serum* remained turbid under the same conditions. All tests were performed in triplicate and similar results were obtained.

5. PROTHROMBIN UTILIZATION TESTS. *Drug-sensitive serum* produced marked inhibition of prothrombin consumption; however, normal serum and *drug-insensitive serum* failed to demonstrate this inhibition (Table 2).

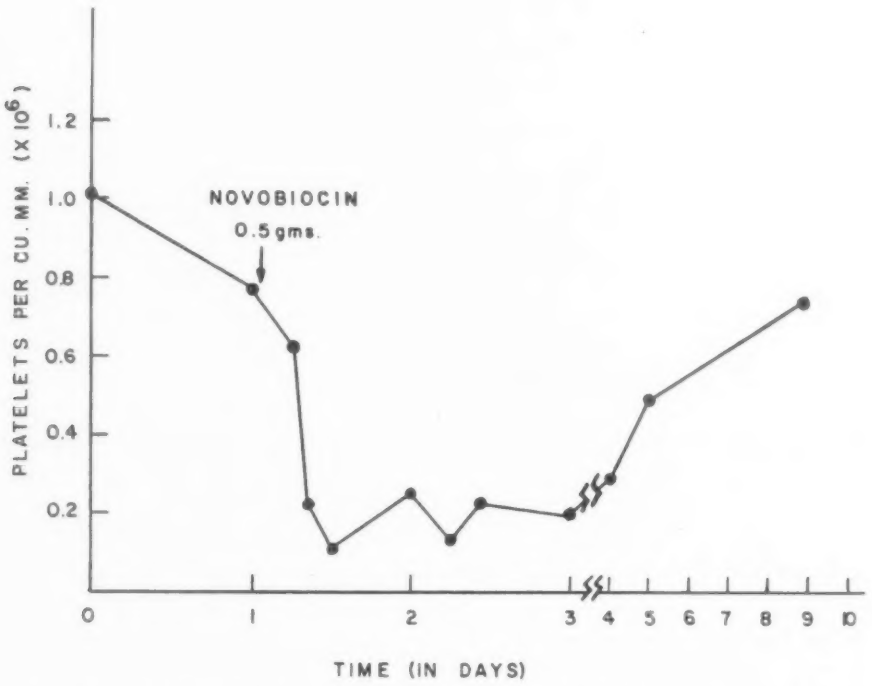

Fig. 2.—This graph illustrates the response of the patient's platelet levels after the administration of 500 mg. of novobiocin.

6. THROMBOPLASTIN GENERATION TESTS. Prior to the readministration of the drug, the patient had a normal thromboplastin generation time (10.0 sec.). Following the administration of the test dose of novobiocin, the thromboplastin generation time increased (19.0 sec.). When the final platelet suspension of the blood (obtained after the test dose had been given) was concentrated to approximately 800,000

platelets per c.mm., the generation time returned to normal (10.5 sec.). Thromboplastin generation tests are reported in Table 3.

7. PATCH TESTS. All of the patch tests were negative in both the acute and the recovery phases.

Discussion. That novobiocin is a drug with a high incidence of toxic side reactions is well known. Bridges,

TABLE 1.—SHOWING THE INHIBITION OF CLOT RETRACTION BY COMBINATIONS OF NOVOBIOCIN AND *SENSITIVE* (ANTIBODY CONTAINING) BLOOD OR SERA

Sample	*% Clot Retraction*
Control blood 1.0 ml. + 0.2 ml. saline	65
Drug-sensitive blood 1.0 ml. + 0.2 ml. saline	20
Drug-insensitive blood 1.0 ml. + 0.2 ml. saline	65
Control blood 1.0 ml. + 0.1 ml. *drug-sensitive serum* + 0.1 ml. novobiocin solution	0
Drug-sensitive blood 1.0 ml. + 0.2 ml. novobiocin sol.	0
Control blood 1.0 ml. + 0.1 ml. control serum + 0.1 ml. novobiocin solution	65
Control blood 1.0 ml. + 0.1 ml. *drug-sensitive serum*° + 0.1 ml. saline	30

°The inhibition noted may be due to the presence of small quantities of novobiocin in this serum.

TABLE 2.—SHOWING THE EFFECT UPON PROTHROMBIN CONSUMPTION OF COMBINATIONS OF NOVOBIOCIN AND SENSITIVE (ANTIBODY CONTAINING) SPECIMENS

Blood (1.0 ml.)	*Serum Prothrombin Time (sec.)*
Drug-insensitive + 0.2 ml. saline	50
Drug-sensitive + 0.2 ml. saline	13
Control + 0.1 ml. saline + 0.1 ml. of novobiocin solution	60
Control + 0.1 ml. *drug-sensitive serum* + 0.1 ml. of novobiocin solution	20

TABLE 3.—THROMBOPLASTIN GENERATION TIME

Min.	*Control Platelet Suspension (Sec.)*	*Patient's Platelet Suspension (Sec.)*	*Adjusted Patient's Platelet Suspension (Sec.)*
1	57.0	69.0	50.0
2	26.0	60.0	24.0
3	15.0	35.0	18.0
4	11.5	20.0	12.0
5	10.0	19.0	11.0
6	10.0	19.0	10.5

Berendes, and Good[5] showed a 12.7% incidence of serious reactions to this antibiotic. Almost invariably these patients were on relatively large doses of novobiocin, usually 2.0 gm. per day. The toxic skin reactions usually occurred between the sixth and ninth day of therapy. In the case history reported above, the rash and fever appeared on the eighth day while the patient was receiving a dosage of 2.0 gm. daily. In addition to developing a rash, typical of novobiocin toxicity, this patient developed purpura which was proven to be on an immunothrombocytopenic basis associated with novobiocin administration.

Although immunothrombocytopenia induced by sensitivity to novobiocin has not been reported, 2 patients with thrombocytopenia in which novobiocin has been implicated as the causative agent (Lawrence[12]) have come to our attention. The first patient received 2.0 gm. of novobiocin daily for 13 days, at which time the platelet count had decreased to 56,000 per c.mm. The platelet count returned to normal within 3 days following discontinuation of novobiocin therapy. In the second case, 0.5 gm. of novobiocin was administered daily. On the fifth or sixth day purpura, arthralgia, headache, and fever appeared. The platelet count decreased to a level of 12,000 per c.mm. The symptoms regressed 2 days following withdrawal of novobiocin and treatment with prednisolone. No attempts were made to elucidate the mechanism of the thrombocytopenia in these patients.

Some potential danger is associated with the readministration of a drug to a sensitive individual, as has been shown in the instances of Sedormid and quinidine purpuras (Ackroyd[1], Larson[11]). Considering the prompt and dramatic rise in platelet levels of this individual in response to withdrawal from the drug or to steroid therapy, novobiocin was readministered to this patient with her full understanding and cooperation. Except for a minor degree of pruritus, she felt no ill effects. No evidence of bleeding was noted except that the tourniquet test, previously negative, became strongly positive and remained so until recovery. The length of time required for the return of the platelet count to normal levels would seem to agree with the results published for quinidine-induced thrombocytopenia (Barkham and Tocantins[3]).

In the study of the mechanism of thrombocytopenia in our patient we have used methods employed in previous investigations of drug-induced thrombocytopenias (Ackroyd[1], Freedman, Brady and Barr[10], Larson[11], Stefanini *et al.*[16]). From the results of *in vivo* experiments performed upon this patient it has been shown rather conclusively that a thrombocytopenia has been reproduced in response to novobiocin readministration. Of the *in vitro* methods employed, microscopic agglutination and lysis of normal platelets was demonstrated in the presence of the patient's *drug-sensitive plasma* or *drug-sensitive serum*. By means of inhibition of clot retraction, impaired prothrombin utilization, and accelerated optical clearing of platelet-rich plasma, an alteration of platelet function or behavior in the presence of antibody was shown.

In the first of these tests, the tubes containing the patient's *drug-sensitive* blood (obtained during the period of thrombocytopenia) showed defective clot retraction without the addition of any drug. Upon the addition of novobiocin solution, further inhibition of clot retraction was noted. This result was similar to the results obtained in

the sample in which novobiocin and the patient's *drug-sensitive serum* were added to control blood. The addition of novobiocin solution alone to control blood showed no inhibition of clot retraction.

The same effect was noted in the prothrombin utilization test; that is, the addition of the patient's drug sensitive serum and novobiocin to control blood impaired prothrombin utilization. The differences noted between *drug-insensitive* and *drug-sensitive* bloods probably were due to the lowered platelet concentration of the latter which was obtained at the time of thrombocytopenia. Novobiocin itself had no effect upon prothrombin consumption of control bloods.

Of the standard tests for platelet function performed on this patient's blood, the thromboplastin generation test was most interesting. When the patient's platelet suspension contained approximately 150,000 platelets per c.mm., thromboplastin generation was abnormal; whereas, if the platelet suspension was concentrated to approximate that of the control suspension (800,000), thromboplastin generation then became normal. This would indicate that the defect produced by novobiocin is a quantitative defect, and not a qualitative one. Thus the adsorption of the antibody upon the platelet does not interfere with the platelet phase of thromboplastin generation.

Ackroyd[2] has presented the hypothesis that the mechanism involved in Sedormid purpura is that of a union of the platelets with the drug which, acting as a hapten, confers antigenic properties upon the platelets. He also postulates that this union is extremely labile and, when the drug is removed by washing, the platelets, being no longer antigenic, separate from the lytic factor. Such a mechanism has been invoked in quinidine-induced thrombocytopenia (Barkham and Tocantins[3], Freedman, Brady and Barr[10], Larson[11], Stefanini *et al.*[16]). The data presented above indicate that this same mechanism may also be involved in novobiocin-induced purpura.

Summary. A case history of an immunothrombocytopenia caused by novobiocin is described. Sensitivity to novobiocin was substantiated by reproducing a thrombocytopenia with readministration of this drug. Platelet agglutinins and lysins were demonstrated in the patient's blood plasma and serum. Immunologically adapted clot retraction, prothrombin utilization, and optical clearing tests showed evidence of impaired platelet function. Evidence is presented that the defect is a quantitative one and does *not* interfere qualitatively with thromboplastin generation.

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SUMMARIO IN INTERLINGUA

Immunothrombocytopenia Inducite Per Novobiocina

Es presentate le historia de un caso de immunothrombocytopenia causate per novobiocina. Le sensibilitate a novobiocina esseva corroborate per reproducer thrombocytopenia per un re-administration del droga. Agglutininas e lysinas plachettal esseva demonstrate in le plasma sanguinee del patiente e etiam in su sero. Le retraction del coagulo (in adaptation immunologic), le utilisation de prothrombina, e le clarification optic esseva testate e indicava un imperfection del function plachettal. Es presentate datos que pare provar que le defecto es quantitative e que illo *non* affice le qualitate del generation de thromboplastina.

TREATMENT OF AMBULATORY HYPERTENSIVE PATIENTS WITH TRIMETHIDINIUM METHOSULFATE

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The plethora of commercially available antihypertensive agents and publications concerning treatment reflect both the importance of the problem as well as difficulties encountered in its complete solution. Despite difficulties in recognizing the hypertensive etiologic factors, progress in medical treatment has produced gratifying results in most cases. There remains a group of severely hypertensive patients who respond, if at all, only to combination therapy utilizing ganglionic blocking agents. These currently available drugs differ chemically but therapeutically have the same physiologic action and despite adequate lowering of the blood pressure they sometimes present such discomforting by-effects as to preclude practical usage.

It is the purpose of this report to present the therapeutic results in an ambulatory group of patients with severe diastolic hypertension. A new compound possessing ganglionic properties, but demonstrating, in addition, a central component of antihypertensive activity, was utilized in this clinical evaluation. This drug, trimethidinium methosulfate,* is an asymmetric bis-quaternary amine. The pharmacology of trimethidinium has been studied by Klupp[5], Eckfeld, Tislow and Seifter[3], and Hosko, Townsend, Tislow, and Seifter[4].

Methods and Materials. From a group of 50 patients receiving trimethidinium, 38 have received the drug for a sufficient time to formulate certain opinions. All patients were profiled in the usual manner and evaluated at 1- to 2-week intervals as indicated in a similar group previously reported[2]. All patients presented a resting diastolic pressure of at least 120 mm. Hg as indicated by hospital blood pressures and clinic records, augmented in many cases by determinations made in the home by the patient or his family. As indicated in Table 1, 30 patients presented

TABLE 1.—PATIENT SELECTION

Total Patients		38	
Females		22	
Males		16	
Negro		33	
Caucasian		5	
Average Age		47.5	years
Smithwick Classification	I	0	patients
	II	6	"
	III	8	"
	IV	24	"
Etiology	Primary	30	"
	Renal	4	"
	Toxemia	4	"

*Trimethidinium methosulfate will be available as Ostensin, Wyeth Laboratories, Inc., Philadelphia, Pa.

no evident cause for their blood pressure elevations and were classified as primary[1]. Four patients had changes suggestive of pyelonephritis on intravenous urography and were classified as renal despite repeated negative urine cultures. Four patients presented a past history of toxemia of pregnancy.

Twenty-seven of the patients experienced a previous clinical trial with at least one ganglionic blocking agent and were transferred to trimethidinium because of poor results or excessive pharmacologic by-effects. The duration of trimethidinium therapy varied from 3 to 11 months with an average of 7.7 months. Dosage of trimethidinium was instituted with 20 mg. before breakfast and 20 mg. at bedtime. In the absence of adequate blood pressure reduction, a third dose was added in mid-afternoon. All doses were increased by 20 mg. at each clinic visit until an optimum decrease in blood pressure was attained.

All 38 patients had received reserpine in doses of from 0.25 to 0.5 mg. daily for a period of 1 to 14 months. This medication was continued throughout the study except for specific study periods when the drug was temporarily withdrawn.

Because of the preponderance of Negro patients, it was not possible to draw conclusions regarding racial differences in therapeutic results, although 3 of 5 Caucasians had a good response. Likewise, the small group representing renal etiologic factors does not lend itself to statistical analysis. For this reason, the entire group has been considered together.

Results. Early in the study it became evident that trimethidinium was considerably more potent when taken on an empty stomach, hence, each patient was advised to take the initial morning dose prior to breakfast. On this basis, the presence of ganglionic blocking activity was evident, in that all patients at some time or another reflected a reduction in standing diastolic blood pressure of at least 20 mm. Hg. We recognize the inherent errors in evaluating therapeutic success by blood pressure measurements, but have resorted to this device in the absence of a satisfactory substitute. Table 2 reflects the results of therapy. Treatment of diastolic blood pressures represents the average pressure changes found after the initial lowering effect was attained. Dosage of trimethidinium reflects total daily dosage which, in most cases, represents three equal doses in 24 hours. Occasionally, it was found that a larger dose, particularly in the afternoon or evening, would result in less early morning postural symptoms. One patient experienced antihypertensive activity of 10 to 12 hours on a single dose and was most adequately maintained on a twice daily schedule; for example, first dose before breakfast and the second in the evening. Therapeutic success should reflect not only the attainment of normal diastolic pressures, but also consistency of this result on repeated clinic visits. Thus, a patient who only occasionally became normotensive was graded as having a poor result because of inconsistency.

Treatment response in most cases appeared to follow three stages:

I. Stage of Sensitivity: This stage is characterized by considerable antihypertensive response on the relatively small dose of 20 to 40 mg. of trimethidinium given initially and persists 1 to 4 weeks.

II. Stage of Relative Tolerance: Following the initial phase diastolic pressures would frequently resume control levels despite considerable dosage increase.

III. Therapeutic Phase: Upon attaining a given dosage of trimethidinium, which in our patients averaged 157.9 mg. per day, sensitivity was again demonstrated. This renewed sensitivity has been present as long as 7 months in our patients without return of tolerance.

It is of great importance that trimethidinium should not be discontinued during the phase of tolerance since a good result is to be expected

TABLE 2.—THERAPY RESULT (38 PATIENTS)

Study duration (range)		3 to 11 months
Study duration (average)		7.7 months
Trimethidinium dose range		40 to 520 mg./day
Trimethidinium dose average		157.9 mg./day
Ave. diastolic blood pressure fall		32 mm. Hg
Consistency of Normotension	Poor	5%
	Intermediate	58%
	Good	37%

upon increase of dosage. Of particular interest in those attaining a good therapeutic result was a tendency to attain normotension with relatively little postural change, which suggests a possible central activity. This activity probably differs from that of reserpine, since we were able to note the potentiating action of reserpine in substitution experiments. Chlorothiazide also enhances the antihypertensive action of trimethidinium.

TABLE 3.—TRIMETHIDINIUM BY-EFFECTS (38 PATIENTS)

Symptom	*No. of Patients*	*%*
Postural	14	36.8
Visual	13	34.2
Constipation	2	5.3
Weakness	2	5.3

The final practicability of the use of a ganglionic blocking agent rests upon the incidence of pharmacologic by-effects. Since these distressing symptoms frequently mimic those of uncontrolled hypertension they prove to be alarming to patient and physician alike. The incidence of such symptoms in this group is indicated in Table 3. It should be noted, however, that these symptoms frequently coincide in a single patient and that in others are entirely absent. Postural hypotension symptoms in our experience are the most common and, of all by-effects, most accurately reflect adequate dosage. The visual disturbances noted were transient in approximately half the patients and, when not self limiting, usually responded to oral pilocarpine nitrate in doses of 2.5 to 5 mg. three times a day. Of particular interest has been the virtual absence of constipation despite adequate blood pressure control. This finding suggests a lower risk of paralytic ileus as compared to other ganglionic blocking agents. Additional symptoms encountered were dry mouth, weakness and impotence. No evidence of acute chronic toxicity has been encountered with this drug.

TABLE 4.—COMPARATIVE RESULTS OF THERAPY IN 27 PATIENTS

		Blood Pressure Control With Trimethidinium			*By-effects With Trimethidinium*		
Previous Drug	*No. Pts.*	*Better*	*Same*	*Worse*	*Better*	*Same*	*Worse*
Mecamylamine	15	8	6	1	6	9	0
Chlorisondamine	7	4	1	2	4	3	0
Pentolinium	5	2	1	2	2	3	0
TOTAL	27	14	8	5	12	15	0

Twenty-seven patients had previ-

ously received treatment with a different ganglionic blocking agent. Table 4 indicates comparative results. When interpreting these results favorable to trimethidinium, caution must be exercised not only because of the small number of patients considered, but also because patients frequently exhibit dosage limitations because of troublesome by-effects on one agent which do not necessarily appear with another. Some significance should be attached, however, since the selection of poorly controlled patients generally imposes a rigid test on a new therapeutic agent.

Conclusions. Trimethidinium was administered to 38 severely hypertensive patients for a period of 3 to 11 months. In a dose range of from 60 to 520 mg. daily, it was found to be an effective antihypertensive agent. The average diastolic fall was 32 mm. Hg and 37% of this group were maintained with consistent normotensive levels. Fifty-eight per cent of the remaining patients showed normotension, but less consistently. The mechanism of action appears to involve ganglionic blockade primarily, although an additional central action is suggested. Pharmacologic by-effects are similar to those of other ganglionic blocking agents with the exception that effects on the gastrointestinal tract appear markedly reduced. Reserpine and chlorothiazide were found to be synergistic with trimethidinium.

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SUMMARIO IN INTERLINGUA

Le Tractamento De Ambulatori Patientes Hypertensive Con Methosulfato De Trimethidinium

Trimethidinium esseva administrate a 38 severmente hypertensive patientes durante periodos de inter 3 e 11 menses. In le doses usate, inter 60 e 520 mg per die, illo se monstrava un efficace agente antihypertensive. Le reduction diastolic medie esseva 32 mm de Hg. Trenta-septe pro cento del gruppo esseva mantenite a nivellos continuemente normotensive. In 58% del remanente patientes, normotension esseva effectuate, sed minus uniformemente. Le mechanismo del action del droga pare esser primarimente un question de blocage ganglionic, sed le possibilitate es signalate que il existe additionalmente etiam un action central. Le effectos lateral es simile a illos de altere agentes de blocage ganglionic, excepte que le effectos gastrointestinal es marcatemente reducite. Esseva trovate que reserpina e chlorothiazido es synergic con trimethidinium.

LOW SERUM POTASSIUM LEVEL IN SEVERE HYPERTENSION

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A NUMBER of reports of recent years have established the occurrence of a new clinical picture termed primary aldosteronism or Conn's syndrome (Conn and Louis[2]), caused by overproduction of the highly active mineralocorticoid, aldosterone. The clinical picture is characterized by intermittent pareses, paresthesias, in some cases tetanic convulsions, polyuria, and hypertension. Aldosterone causes sodium retention and loss of potassium; this will give rise to a slightly increased serum sodium level with alkalosis and hypochloremia and, as the most important anomaly, a low serum potassium level.

As it had thus been recognized that hypertension may be a feature of primary aldosteronism, we have determined the serum potassium level in a number of patients with essential hypertension. It will be mentioned below that a lowered serum potassium level may be found in severe cases, while they present no other evidence of a primary disorder of the adrenal glands.

Material and Results. Serum potassium determinations were made in 32 patients with untreated essential hypertension. The values are given in Table 1.

Normally the serum potassium level is between 3.9 and 5.0 in 80% and between 3.5 and 5.6 mEq. per L. in 98% (Wootom and King[13]).

In patients in whom the examination of the retina showed no or slight to moderate changes the potassium values were within the normal limits; in 2 cases they were near the lower limit of the normal.

TABLE 1.—SERUM POTASSIUM VALUES IN 32 PATIENTS WITH UNTREATED ESSENTIAL HYPERTENSION

Eye Ground Changes	*Number of Patients*	*Serum Potassium, mEq./L.*	
		Ranges	*Mean*
No changes or K & W I	10	3.9–5.3	4.5
K & W II	5	3.6–4.5	4.0
K & W III without cotton wool exudates	3	3.6–4.5	4.1
K & W III with cotton wool evudates	7	3.3–4.5	3.9
K & W IV	7	2.6–4.4	3.4

However, of 7 patients with cotton-wool exudates in the retina, one had a pathologically lowered serum potassium level; and in 7 patients with choking of the discs a low level was found in 4. These two groups of patients will, therefore, be described in greater detail.

As already mentioned, all patients were untreated when admitted to the

department. The serum potassium determinations were repeated later on after treatment with antihypertensive drugs had been instituted.

Table 2 shows the values of serum potassium and certain clinical data in the 14 patients with severe changes in the eyegrounds. Figure 1 shows the serum potassium levels before and during treatment compared with the normal values mentioned above.

The patients were subjected to antihypertensive treatment with one or more of the following drugs: Reserpine, hydralazine, pentolinium and mecamylamine.

In the course of this treatment the lowered serum potassium values rose to normal except in 2 patients (see below). These normal values were established in the course of a few weeks to 3 months. In those patients in whom frequent determinations were performed, the values seemed to rise gradually as the fall in blood pressure occurred.

The 2 patients in whom normal values were not achieved were Cases 2 and 12. In the first of these the blood pressure could not be satisfactorily lowered in spite of energetic treatment and the patient died after 1½ years. In the other, the patient's uremia increased during the course of treatment, and death occurred after 6 weeks. Necropsy showed no signs of adrenal disorder in either of these 2 patients.

Unfortunately, determinations of serum sodium, chloride and bicarbonate levels were not made in all our cases. These values are available, however, in the 4 patients with grade IV retinal changes and an especially low serum potassium level. In 2 of these, low serum chloride and high serum bicarbonate levels were found, as would be true of primary aldosteronism. One of these 2 patients had been vomiting.

Discussion. In explaining the observed hypokalemia in untreated, severe cases of hypertension, several possibilities must be considered.

Hypokalemia cannot simply be a consequence of vomiting or diarrhea; only one patient (Case 5) vomited within a few days of the first potassium analysis; none of the patients had diarrhea.

A few cases of hypokalemia have been described in whom an abnormal loss of potassium through the kidneys has been considered the primary cause of the condition. In all probability, however, several of these have been cases of primary aldosteronism and the existence of an isolated, primarily renal, hypokalemia is, therefore, disputable. Furthermore, these cases differ from ours owing to the fact that hypertension was absent in several, and that the serum potassium could be raised only by the administration of large doses of potassium salts.

The possibility that our patients may have had a primary aldosteronism can presumably be excluded solely by the fact that the low serum potassium level soon became normal in the course of effective antihypertensive treatment. Furthermore the patients did not present the other clinical signs seen in Conn's syndrome.

We did not determine the aldosterone excretion in our patients. In 1951, however, Luetscher and Deming[9] mentioned that they had found a highly active, sodium-retaining corticoid in patients with hypertension. Genest *et al.*[3] have recently reported that in 13 patients with hypertension, including 6 with malignant hypertension, they found a slightly increased aldosterone excretion. They mentioned no serum potassium values.

It is thus possible that there is an increased output of aldosterone in cases of severe hypertension. This will

TABLE 2.—SOME CLINICAL AND LABORATORY DATA IN 14 CASES OF SEVERE ESSENTIAL HYPERTENSION

No.	*Sex*	*Age*	*Blood-pressure*	*Eye Ground*	*Serum Creatinine mg./100 ml.*	*Serum Potassium mEq./L*	*Serum Potassium During Treatment mEq./L*
1	♀	44	280/185	IV	(34) (blood urea)	2.9	3.8
2	♀	35	250/145	IV	1.7	2.6	3.0
3	♂	54	220/120	IV	1.2	4.4	4.5
4	♂	41	250/160	IV	4.2	2.7	4.8
5	♂	39	220/140	IV	1.1	3.2	4.0
6	♂	51	200/120	IV	2.4	3.5	4.5
7	♂	59	250/150	IV	2.4	4.3	4.5
8	♀	48	225/135	III	1.3	4.0	4.6
9	♀	58	300/150	III	1.9	3.8	4.6
10	♂	60	215/120	III	1.7	4.5	3.9
11	♂	55	230/140	III	1.6	4.2	5.0
12	♀	48	250/150	III	2.3	3.8	3.2
13	♀	67	270/125	III	1.2	3.7	4.2
14	♂	46	230/140	III	1.1	3.3	4.3

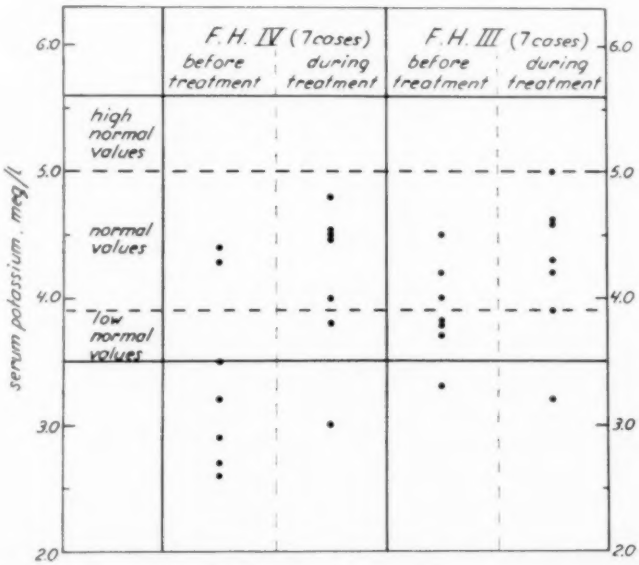

Fig. 1.—Serum potassium values in 14 cases of severe essential hypertension before and during medical treatment.

lead, in the most severe cases, to sodium retention and increased potassium excretion with significant lowering of the serum potassium level.

It has long been known that an unimpaired adrenocortical function is a necessary condition for producing experimental renal hypertension (Goldblatt[1]). In this type of hypertension, furthermore, sodium retention has been observed, causing an increase of the extracellular space (Braun-Menendez and Martinez[1] and Grollman and Shapiro[8]), which might suggest hyperactivity of the adrenal cortex.

Selye[12] states that an increase in the ratio of serum sodium to serum chloride may be found in hypertension. Perera and Blood[10] have shown that sodium chloride restriction results in less weight loss in hypertensive than in normal individuals. Both of these observations are compatible with the assumption of increased adrenocortical activity.

The cause of any possible increased aldosterone production in patients with hypertension may simply be that the rise in blood pressure, in itself, produces a tendency to increased Na-excretion, as shown experimentally by Selkurt[11] and determined in man by Green and coworkers[5,6,7]. The increased sodium loss leads then, by a regulatory mechanism, to increased production of sodium-retaining factors. It is doubtful whether there is an *additionally* increased aldosterone production which in some way or other forms part of the pathogenesis of essential hypertension. Some of the observations referred to above, however, might suggest that this is so.

We wish to present this preliminary report on lowered serum potassium level in severe hypertension, *inter alia*, for merely practical reasons. After it has become generally known that hypertension may be due to primary aldosteronism, determinations of the serum potassium level will be included in routine investigations of hypertensive patients. It seems important to know that abnormally low serum potassium values may be found in severe hypertension, and that these values are reversible and apparently not produced by a primary disorder of the adrenal glands.

Summary. Determination of serum potassium was performed in 32 cases of untreated essential hypertension.

Low values were found in severe cases. Of 14 cases, including 7 with papilledema, 4 had low normal values 3.5 to 3.8 mEq. per L.), and 5 had abnormally low values (below 3.5 mEq. per L.).

During successful treatment with antihypertensive drugs the serum potassium rose to quite normal values (over 3.8 mEq. per L.) in the course of a few weeks to 3 months.

The observed hypokalemia could not be ascribed to vomiting or diarrhea, nor could it be due to chronic renal disease or primary aldosteronism. Several experiences from experimental and human hypertension support the view that adrenocortical function contributes to the pathogenesis of essential hypertension. A slightly increased aldosterone excretion has recently been found in patients with hypertension. Our low serum potassium values may, therefore, be due to an increased production of aldosterone.

As hypertension may be caused by primary aldosteronism, serum potassium determinations will become part of routine investigation in severe hypertension. It is important to know, we believe, that such cases may show low serum potassium values which are reversible on treatment and seemingly not due to adrenocortical disease.

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SUMMARIO IN INTERLINGUA

Basse Nivello Seral De Kalium In Hypertension Sever

Determinationes del nivellos seral de kalium esseva effectuate in 32 casos de non-tractate hypertension essential.

Basse valores esseva trovate in casos sever. Ex 14 casos, incluse 7 con papilledema, 4 habeva valores basse normal (3,5 a 3,8 mEq per L) e 5 habeva valores basse anormal (infra 3,5 mEq per L).

Durante un tractamento successose con drogas antihypertensive, le nivello del kalium seral montava usque a valores satis normal (*i.e.*, a plus que 3,8 mEq per L) in le curso de inter plure septimanas e 3 menses.

Le hypokalemia de iste patientes non poteva esser attribuite a vomito o diarrhea, e illo etiam non poteva esser le effecto de chronic morbo renal o de aldosteronismo primari. Observationes in hypertension experimental e etiam in hypertension de patientes human supporta le opinion que le mechanismo adrenocortical contribue al pathogenese de hypertension essential. Leve augmentos del excretion de aldosterona ha recentemente essite constatate in patientes con hypertension. Per consequente il es possibile que nostre basse valores pro kalium seral es le resultato de un augmento in le production de aldosterona.

Viste que hypertension pote esser causate per aldosteronismo primari, il es a expectar que le determination del nivello de kalium seral va devenir un parte del investigation routinari de hypertension sever. Il es importante saper que tal casos monstra a vices basse valores pro le kalium seral e que iste valores, apparentemente non causate per morbo adrenocortical, pote esser revertite per le tractamento del hypertension.

CAPILLARY CHANGES INDUCED BY MOTOR AND SENSORY STIMULI IN UNILATERAL DISEQUILIBRIUM

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In the neurological syndrome of sensorimotor induction in unilateral disequilibrium (Halpern[3]) changes in postural pattern modify sensory functions despite the anatomical integrity of the sense organs. This syndrome is also characterized by the mutual influence of motor and sensory functions. Thus, the disturbances present are influenced differently by changes in head posture, by opening and closing of the eyes and by the alternate opening of each eye. The various disturbances are also influenced by colors in that blue ameliorated and red aggravated them. Special examinations revealed that changes in head posture, state of the eyes and color stimuli influenced not only the functions of the central nervous system but also the autonomic functions of respiration and circulation (Halpern, Braun and Eliakim[4]). The aim of the present study was to examine if the human capillaries are also influenced by the same experimental procedures.

Case Report. NEUROLOGICAL BACKGROUND. A woman, aged 27, had a 7-year history of right-sided disequilibrium with the features of sensorimotor induction, as a manifestation of disseminated sclerosis. As the full clinical picture and relevant literature have been reported (Halpern[3]), it will here suffice to give the pertinent features in this patient. These were: 1) right-sided postural deviation of the whole body and the homolateral extremities, 2) right-sided visual displacement of spatial coordinates with ipsilateral macropsia, 3) deviation to the right in tactile and haptic localization, 4) right-sided macrosteriognosia and overestimation of weight when using the right hand, 5) the influence of motor and sensory stimuli on the disturbed equilibrium and the induced sensory disturbances.

These sensorimotor disturbances were aggravated when both eyes were closed, when only the right homolateral eye was kept open, under the influence of a red filter and when the head was turned to the contralateral left side. In contrast, these disturbances were corrected when both eyes or only the contralateral left eye were open, when a blue filter was used or when the head was turned to the homolateral right side.

METHOD. The capillaries of the nailbed were examined by capillary microscopy at a magnification of 60 (Davis[1]). The capillaries were photographed by attaching a Leica camera to the 6X eyepiece. The diameter of the capillaries was measured by a scale incorporated in the eyepiece, the absolute value of the distance between divisions having been measured (Landau and Davis[7]).

The capillaries were first studied with the patient's head in her spontaneous position, that is, inclined a little to the right (a) with both eyes of the patient open and (b) with both eyes closed, then (c) with her head turned to the homolateral right side, and (d) with her head turned to the contralateral left side, and (e) after placing blue and red glasses in turn over the left eye. The color filters employed were Kodak Wratten blue No. 47 and red No. 29.

Results. The capillaries of the selected nailbed were examined with the patient's head in her spontaneous posi-

tion, with both eyes open until their shape, diameter, color and the character of the blood flow were thoroughly familiar. The capillaries were of normal length and contour, rather thinner than the normal with a diameter of 4.5 to 5.0 μ (Fig. 1) as compared with the normal range of 5 to 12 μ. Blood flow was normal. There was no red-cell aggregation.

CLOSING EYES. The patient was then examined with both eyes closed. After 10 seconds there was capillary thinning which was very marked in 15 seconds, and in 20 seconds the thinning was accompanied by intracapillary red-cell aggregation. After 2-minutes' rest with open eyes the capillaries were again examined with both eyes closed. After 10 seconds the flow was slowed, after 30 seconds there was thinning to 3.5 μ diameter, after 60 seconds thinning with red-cell aggregation. At 75 seconds the patient was asked to open both eyes and at 120 seconds the capillaries were returning to normal.

On closing the eyes a third time, after 2-minutes rest, thinning took place after 40 seconds and returned to normal 30 seconds after opening both eyes. Doing the experiment for the fourth time produced thinning and red-cell aggregation 30 seconds after closing both eyes. The thinning persisted all the time the eyes were closed, a period of 1½ minutes, but this time the capillaries did not return to normal until 4 minutes after opening the eyes.

HEAD TURNING. The capillaries were next examined with the patient's eyes open and the head turned first to the right and then to the left. When with both eyes open her head was turned to the right homolateral side for one minute there was no significant change in the diameter of the capillaries. Her head was then turned to the left contralateral side. After 45 seconds there was thinning of the capillaries to 3.5 μ with interruptions in the blood stream. After 75 seconds there was very marked thinning to 2.5 to 3.0 μ (Fig. 2) which persisted until the head was turned to the normal position 4 minutes from the start of the experiment. Two minutes later the capillaries were returning to normal and half a minute later were quite normal.

COLORED GLASSES. The patient closed the right eye and the blue glass was put over the left eye for one minute. There was virtually no change in the capillaries. After 3-minutes interval a red glass was put over the left eye in place of the blue. Marked thinning to 3.0 μ took place after 1½ minutes and persisted all the time the red glass was over the eye. After 3 minutes the red glass was replaced by blue and in one minute the capillaries returned to normal.

In the next experiment the left eye was closed and the blue glass put over the right eye for 30 seconds, and then was replaced by the red glass. Forty-five seconds later capillary thinning was extreme and there was virtual disappearance of capillaries. The red glass was replaced by blue after 3 minutes and it was not until the blue glass was in position for 2½ minutes that the capillary diameter returned to the initial state.

The above procedures were repeated after a few days, with the same results. In healthy persons closing the eyes or head turning or colored glasses over the eye did not affect the capillaries.

Comment. In the sensorimotor induction syndrome it is of particular interest that the aggravating and correcting effects of the motor and sensory stimuli described above influenced body posture and also the accompanying sensory changes such as vision, hearing, stereognosis, vibration, two-point discrimination and reaction time (Halpern and Kugelmaas[5,6]).

In these patients these procedures

also systematically modified functions of respiration and circulation, namely, respiration, pulse rate, blood pressure, electrocardiogram and ballistocardiogram (Halpern, Braun and Eliakim[4]).

In this patient with the sensorimotor induction syndrome, the present study showed that the capillaries also reacted systematically to the same stimuli. Eye-closing, head turning to the contralateral side, and a red filter in front of the eye induced almost immediately marked thinning of the lumen of the capillaries and also intracapillary red-cell aggregation. The most marked effect followed the application of the red filter which induced such extreme thinning as to render some of the capillaries invisible. When the aggravating stimuli were stopped, the capillaries returned to normal.

In this same patient the aggravating stimuli also induced tachypnea, tachycardia, raised blood pressure, flattening of the T wave in the electrocardiogram and ballistocardiographic changes (Halpern, Braun and Eliakim[4]). Similar changes have been produced experimentally after injections of epinephrine and norepinephrine, while similar capillary changes have been reported after injection of epinephrine (Davis *et al.*[2]). Sustained high blood pressure is often associated with persistent capillary thinning (Landau and Davis[7]).

The effect of these procedures on the capillaries is part of a general pattern of a basic biological mechanism, which

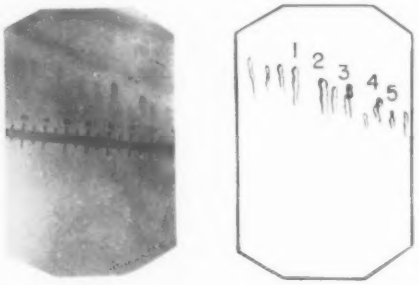

Fig. 1

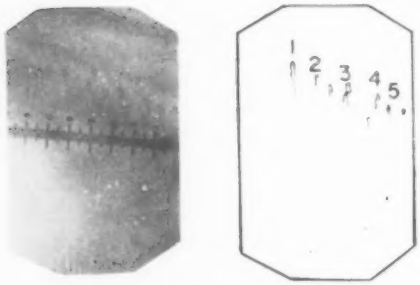

Fig. 2

Figs. 1 and 2.—On the left, photographs of nailbed capillaries. On the right, drawing from photograph.

Fig. 1.—Capillaries of patient in normal state.

Fig. 2.—Capillaries after turning head to the left. Capillaries to the left of No. 1 almost invisible. Capillaries Nos. 1, 2, 3, 4, 5 markedly thinner.

holds not only for the central nervous system but also for the autonomic.

Summary. In a patient with the sensorimotor induction syndrome with right-sided disequilibrium, marked capillary thinning and intracapillary red-cell aggregation were induced by closing of the eyes, turning of the head to the left contralateral side and placing a red filter in front of the eyes. These effects were in keeping with the changes induced by the same stimuli on various functions of the central nervous system and also on respiration and circulation. All these changes were part of a pattern of a general biological mechanism characteristic of sensorimotor induction involving both the central and the autonomic nervous systems.

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SUMMARIO IN INTERLINGUA

Alterationes Capillari Inducite Per Stimulos Motori E Sensori In Disequilibrio Unilateral

In un patiente con le syndrome de induction sensorimotori con disequilibrio dextero-lateral, marcate grados de tenuification capillari e de aggregation intracapillari de erythrocytos esseva inducite per clauder su oculos, per tornar su capite verso le sinistra (le latere contrari), e per placiar un filtro de rubio ante su oculos. Le effectos esseva congruente con le alterationes inducite per le mesme stimulos in varie functiones del systema nervose central e etiam in le respiration e in le circulation. Omne iste effectos esseva elementos in un mechanismo generalmente biologic characteristic de induction sensorimotori afficiente le systema nervose central e le systema nervose autonome.

INUTILITY OF POSITIONS 7 AND 8 IN PRECORDIAL ELECTROCARDIOGRAPHY

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In precordial electrocardiography opinions differ as to the use of chest positions 7 and 8. Position 7 is at the left posterior axillary line; position 8 at the inferior angle of the left scapula. Both are on a horizontal level from position 6, which is at the mid-axillary line in the fifth left intercostal space.

Some recommend the routine use of these positions (Myers[8], Wilson *et al.*[17]). Others advise its use in special situations, especially lesions involving the left border and left lateral aspect of the heart (Sodi-Pallares[14]). Holzman[4] states that V_8 does not have any practical interest. He suggests that V_7 be used as a supplementary lead where the results of the standard program do not correspond to those expected from the clinical examinations, where things are still in doubt, or where the limb leads and chest leads do not appear to allow a consistent interpretation. Sokolow and Friedlander[15] suggest that when V_6 shows complexes of right ventricular origin and right ventricular hypertrophy is being considered, V_7 and V_8 be taken in an attempt to demonstrate if normal left ventricular potentials are present. Partridge[10] found that in some cases of left bundle branch block the complexes of the leads from the left of the precordium were not of the type usually obtained from points to the left of the transitional zone. But he did find complexes of the usual type in 2 of 11 such cases when he obtained additional leads from the left side of the thorax.

Others do not recommend the use of V_7 or V_8 or both. Barker[1] states: "Leads from the posterior aspect of the thorax have not proved to be of a great deal of clinical value. Since they are located as far or nearly as far away from the cardiac surfaces as the root of an extremity, they contain deflections which are inconveniently small. This is likely to be the case when the patient is in the prone position and when the heart drops forward." Margo and Foscarini[7] studied leads V_7 and V_8 in 100 cardiac patients and found them so variable that they were unable to correlate them with the clinical picture. Rosenman *et al.*[11] found that V_7 was not required in the presence of leads aVl and aVf.

The present study is concerned with the value of positions 7 and 8 as compared with position 6 in clinical electrocardiography. It includes (1) 705 individuals without heart disease from age 20 to 85; (2) 778 who had (a) left heart strain as is encountered in hypertensive heart disease, aortic ste-

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osis and aortic insufficiency; (b) recent or old myocardial infarction; (c) coronary artery insufficiency and (3) digitalis effect on the S–T segment in 100 electrocardiograms. Records of bundle branch block were excluded. In every case the usual leads, which included I, II, III, aVr, aVl, aVf, and V3r–V6, were recorded. Table 1 lists the conditions studied and the number of individuals in each group.

TABLE 1.—CONDITIONS STUDIED

Classification	*No. of Cases*
Normal	705
Myocardial infarction	255
Left ventricular strain	331
Coronary artery insufficiency	192
Digitalis effect	100

Table 2 gives the age and sex distribution of the 705 subjects without organic heart disease. The pattern in V_7 and V_8, in general, was very similar to that of V_6. However, the comparative value of positions 7 and 8 was minimized by the low voltage of the T wave recorded in such individuals. It was very often isoelectric and in 2 instances was inverted in V_8. Others, too, have encountered similar difficulties which have discouraged them from using these positions routinely. Grewin[3] states that the T wave in V_7 is so low normally that it may be difficult to decide whether, in any given tracing, it should be regarded as normal, borderline or abnormal. He found also that position 7 is less sensitive than position 8 which is not only more difficult to take, but which may normally give an inverted T wave. We agree with Grewin's conclusion. Leatham[6] studied V_1–V_7 in 100 healthy adults from 18 to 71 years of age and found an inverted T in V_7 in one instance. Soulie, Michel and Baygin[16], in normal subjects found a deep Q in V_8 in vertical hearts and a negative T in V_8 in semi-vertical hearts. Lambert[5] studied 33 normals and found that in $V_{7\text{-}8}$, the T wave was usually upright but occasionally flat. Simonson[13] in a study of the distribution of cardiac potentials around the chest in 103 normal men found that the so-called left ventricular epicardial pattern (qR, T) changes in direction to the mid-line of the back so that the T waves may become inverted when the R wave is still relatively large, with a prominent Q wave. He contends that using the criteria of other leads (V_6, V_L or V_f) may lead to a false diagnosis of coronary insufficiency or posterior lateral infarction in regions $V_{7\text{-}9}$ in an appreciable number of normal subjects.

TABLE 2.—AGE AND SEX DISTRIBUTION (NORMAL)

	Sex	
Age	*Male*	*Female*
20–29	38	35
30–39	78	43
40–49	102	71
50–59	98	86
60–69	59	59
70–79	17	15
80–89	4	0
Total	396	309

In this present study we recorded also the electrocardiograms of 255 cases of myocardial infarction, both recent and old. No attempt was made to classify the infarcts on an arbitrary anterior or posterior basis since it served no useful purpose as regards this study. In 106 of the cases signs of the infarction were noted in positions 6, 7 and 8. In 11 cases only V_6 was abnormal. In 136 cases $V_{6\text{-}8}$ were normal. In 2 cases the T wave in V_8 was inverted but was upright and of low voltage in V_6 and

isoelectric in V_7. In all the cases signs of the myocardial infarction were present in the other leads. There was no evidence that V_7 or V_8 helped toward the diagnosis of an infarction. These leads may give information as to the extension of the lesion but it remains to be determined if this has any clinical significance. On the other hand, Grewin[3] states that V_6 does not register posterobasal lesions as effectively as V_7. And, Myers, Klein and Hiratzka[9] state that in cases of posterolateral infarction, abnormal Q wave patterns are not present in V_5 or V_6, or both, when the infarct involves the apical third of the posterolateral aspect of the left ventricle. In such instances, they claim that leads V_7 and V_8 may be abnormal and hence should be taken when the routine leads reveal changes suggestive of either posterior or lateral infarction. Lambert[5] states that, while leads V_7 and V_8 are useful for determining the extent of posterolateral infarcts or for showing unequivocal evidence of posterior or inferior infarcts, he could not answer the question as to whether these leads, in themselves, are useful for the detection of infarcts. But he also states that in some cases of old posterior infarction, the typical features of the infarction pattern had disappeared in the routine leads whereas they were still present in leads $V_{7\text{-}9}$. However, the illustration (Fig. 9 of his paper) that he offered for this contention shows an abnormal V_6, as well as abnormal $V_{7\text{-}9}$. In contrast to the above statement, Shaffer *et al.*[12] state that V_8 may miss evidence of left ventricular disease and that posterior chest leads never constitute the chief evidence of a myocardial infarction.

We analyzed our electrocardiograms of 331 persons who had either hypertensive heart disease, aortic stenosis or aortic insufficiency. In 156 cases the electrocardiograms showed abnormalities characteristic of left ventricular strain in $V_{6\text{-}8}$. In 4 cases V_6 alone was abnormal. In no instance was V_7 and V_8 abnormal when V_6 was normal. In the remainder (171 cases) no abnormalities were present in $V_{6\text{-}8}$. Since there is considerable reduction in the voltage of the QRS–T complexes in $V_{7\text{-}8}$ as compared with V_6, there is a disadvantage in the use of these leads as an aid in the diagnosis of left ventricular strain. Similarly, Rosenman *et al.*[11] studied 112 cases of left heart strain utilizing V_6 and V_7 and found only one instance in which the strain pattern was confined only to V_7.

We analyzed also our electrocardiograms of 192 patients with coronary artery insufficiency, some of whom may have had a myocardial infarction. There were 86 cases in which abnormalities were present in $V_{6\text{-}8}$. In 103 cases, $V_{6\text{-}8}$ were normal. In 2 cases only V_6 was abnormal. In one case only V_6 and V_7 were abnormal. Thus in no instance were $V_{7\text{-}8}$ abnormal when V_6 was normal.

In 100 cases we recorded digitalis effect on S–T segments of the electrocardiogram in leads V_7 and V_8. In every case this was likewise present in V_6.

As a corollary to this study it can be concluded that the exclusive use of position 7 in place of position 6 as recommended (Evans and Hunter[2]) may be misleading.

Summary. Unipolar electrocardiograms were taken in chest positions 7 and 8, as well as in position 6, in 705 individuals, ages 20 to 85, without heart disease; 255 cases of myocardial infarction, recent and old; 331 cases of hypertensive heart disease, aortic stenosis or aortic insufficiency; 192 individuals who had coronary artery insufficiency; and 100 individuals with digitalis effect on the S–T segment of the electrocardiogram.

Since, in individuals without heart disease, the T wave in positions 7 and 8 may show low voltage or be inverted, the routine use of these positions is not encouraged.

Positions 7 and 8 were not of value in the diagnosis of myocardial infarction.

In 331 cases of hypertensive heart disease, aortic insufficiency or aortic stenosis, V_7 and V_8 were never abnormal when V_6 was normal.

In 192 individuals who had coronary artery insufficiency there was no instance where V_{7-8} was abnormal when V_6 was normal.

In 100 cases which recorded digitalis effect on the S–T segments of the electrocardiogram in V_7 and V_8, it was present also in V_6.

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SUMMARIO IN INTERLINGUA

Inutilitate Del Positiones 7 E 8 In Le Electrocardiographia Precordial

Esseva effectuate electrocardiogrammas unipolar in le positiones thoracic 7 e 8 e etiam 6 in (1) 705 individuos de etates de inter 20 e 85 annos sin morbo cardiac, (2) 225 casos de recente e ancian infarcimento myocardial, (3) 331 casos de morbo cardiac hypertensive o de stenosis o insufficientia aortic, (4) 192 individuos con insufficientia de arteria coronari, e (5) 100 individuos con effecto de digitalis super le segmento S–T del electrocardiogramma.

Viste que in individuos sin morbo cardiac, le unda T in positiones 7 e 8 pote exhibir un basse voltage o pote esser invertite, le uso routinari de iste positiones non es recommendate.

Positiones 7 e 8 esseva sin valor in le diagnose de infarcimento myocardial.

In 331 casos de morbo cardiac hypertensive o de insufficientia o stenosis aortic, V_7 e V_8 esseva nunquam anormal quando V_6 esseva normal.

In 192 individuos con insufficientia de arteria coronari, nulle caso esseva incontrate in que V_{7-8} esseva anormal quando V_6 esseva normal.

In 100 casos que registrava effecto de digitalis super le segmentos S–T del electrocardiogrammas in V_7 e V_8, le mesme effecto esseva etiam presente in V_6.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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SOVIET OTOLARYNGOLOGY

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IT has been pertinently observed that Soviet physicians are keenly aware of American developments in medicine but that their American counterparts know very little of Soviet medical activity. In this connection, two advantages accrue to Russian physicians: first, they benefit from a comprehensive information-gathering and translation program that encompasses the world medical literature; and second, so far as concerns American medical literature; the average Soviet investigator possesses a fairly good working knowledge of the English language[11].

Among others, this situation applies to the field of otolaryngology. There are presumably few, if any, American experts on Soviet otolaryngology; apparently, there are only varying degrees of ignorance. To judge from the medical literature, it would be unwise to underestimate or minimize the potentialities of Soviet otolaryngology. American otolaryngologists owe it to themselves to be informed about specific medical activities behind the Iron Curtain. The purpose of this review, the first of its kind, is to summarize for American readers some of the more pragmatic communications reported in the Soviet otolaryngological literature during the present decade.

Soviet otological investigations reveal a variety of interests and activities. Yakovleva[42] studied the taste threshold in 19 patients with Meniere's disease or cochlear-vestibular disturbances induced by vascular disease or cerebral trauma. Alterations were found in taste occurring in Meniere's disease only after an attack. No relationship was

observed between the degree of taste changes encountered and increases in blood pressure measurements.

Siirde and associates[32] describe an investigation whose aim was to fix the threshold of hearing by means of pneumographic registration of respiratory movements. It was found that noise, light and pain stimuli lead to alteration in the rhythm of respiratory movements. At the first perception of sound, respiration is either slowed down or accelerated, and when repeated, the respiratory rhythm is unaffected. The authors believe the procedure can detect true deafness and differentiate it from simulated deafness.

Tchargeyshvili and Tokhadze[35] report that plethysmographic examinations of the left hand and the distal third of the forearm of normal and deaf persons demonstrate that a conditional reflex to sound may be evoked and noted on the plethysmogram. According to Grobshtein[9], disturbances in lipoid metabolism cause lipoid deposits in fibroelastic tissue. Lipoids are deposited in the tympanic membrane, producing rigidity of the drum and lowering of the capacity for sound transmission. The affected tympanic membrane is characterized by yellow-grey turbidity of the central and peripheral areas. The hearing of 54 children, aged 3 to 7 years, was tested by Bukhman[5] with the aid of the skin galvanic reflex. It was concluded that the skin galvanic reflex, with pain as a reinforcement stimulus, can be employed as an objective hearing test, especially in very young children. Minkovskiy[18] asserts that the production of a conditional labyrinthine nystagmus is governed by the cerebral cortex. In this experiment a Barany noise-box was used in conjunction with the rotation of patients. The Barany apparatus was activated at a distance of 15 cm. from the ear and the patient rotated for 10 seconds. Noise and rotation were stopped at the same time. Nystagmus was induced in 2 patients as soon as noise began; occasionally, nystagmus appeared when the patient first saw the Barany apparatus.

Braylovskiy[3] made subcutaneous implants of tissue removed from the spleen and gonads of horned cattle in the abdominal walls of 108 patients with inner ear disease. In some instances, placental tissue and aloes were also implanted. A number of favorable responses were obtained in patients with inner ear disease who previously had malaria, influenza, scarlatina, or typhoid fever. No improvement was detected in the inner ear disease status in patients who had had meningitis, measles, or otosclerosis.

Thirty persons who worked in noisy factories were treated by Krotova[15] with nicotinic acid; 20 to 25 mg. of the substance was administered intravenously three times weekly for a period of 5 weeks. Hearing improved in 22 patients, while no improvement took place in 8 patients. Of 20 patients complaining of tinnitus, the symptom disappeared in 2 patients and improved in six.

Sandrieva[26] describes the successful use of Gramicidin S in chronic otitis media and in postauricular mastoidectomy wounds. Temkin[36] treated a group of 300 patients with such varied findings as vertigo, tinnitus, cough, cephalalgia, vasomotor rhinitis, and pharyngeal pain following tonsillectomy by means of intramucous injections of a 1 to 2% solution of Novocaine into the area of the agger nasi. One or more injections were required. After a lapse of 3 years it was learned that half of the patients with cephalalgia were cured, and of 60 patients treated for the relief of tinnitus, 11 were cured and 16 improved. Some improvement took place among patients afflicted

with vasomotor rhinitis and post-tonsillectomy pharyngeal pain. Ponomariev[23] observed that brucellosis may activate latent nonspecific chronic supparrative otitis media. During 1948, Semenova[28] found that 18 out of 125 patients with mastoiditis had an intact tympanic membrane; in 1949, this finding was observed in 16 out of 87 patients with mastoiditis; in 1950, 26 out of 64 patients; and in 1951, 24 out of 62 patients. A sinking of the superior posterior canal wall was observed in nearly all patients. Despite extensive treatment with sulfonamides, mastoidectomy revealed abundant granulation tissue in the mastoid process.

Ageyeva-Maykova[1] detected diminished hearing, tinnitus, vertigo, disturbance of equilibrium and spontaneous nystagmus in patients with hypertensive disease. Either unilateral or bilateral sympathectomy was performed on 42 patients. Hypertension readings were permanently lowered in 12 patients, with associated disappearance of the cochlearvestibular findings. Sympathectomy produced temporary improvement in 17 patients, while in 6 patients the hypertensive status was unchanged, although vertigo and tinnitus disappeared permanently. Sympathectomy had no effect on 8 patients. Russinova[25] studied 26 cases of cerebral abscess, 11 involving the right temporal lobe, 5 involving the left temporal lobe, 9 attacking the cerebellum, and one case of multiple abscess of the pons varolii. All cases of cerebral abscess were caused by chronic suppurative otitis media, and in most instances they were complicated by meningitis or sinus thrombosis. The patients were treated surgically in combination with sulfonamides and antibiotics. Twenty of the 26 patients recovered.

The findings in a histological investigation of the nasal and olfactory mucous membranes of monkeys (*Macaca rhesus*) when infected by poliomyelitis virus are described by Vinnikov[41]. Seven monkeys underwent infection by the intranasal route, while 11 monkeys, serving as control, were infected via the tonsils. In the latter group, no significant histopathological changes ensued in the nasal mucous membranes. In monkeys infected intranasally, various stages of necrobiosis occurred on the third to the tenth day of the illness, seen mainly in the pseudostratified ciliated epithelium and in the edematous connective tissue. A reactive, proliferative alteration occurred in the sensory nerve endings. Severe destructive changes and edema occurred in the olfactory nerves and olfactory bulbs, in the trigeminal nerves, and in the neurones of the vegetative system.

The nasal mucous membranes of 78 patients afflicted by influenza provided the subject of an inquiry by Fotin[8]. Special attention was paid to vascularity, color of the mucous membranes, and character of the nasal secretions. It was possible to differentiate two groups of patients according to the changes encountered. In one group of 38 patients, characteristic inflammatory changes were discovered; in a second group of 40 patients, hyperemia and exudation were less evident or even absent. The affected mucous membranes were dry and either opalescent blue or cyanotic in appearance. The cyanotic color of the turbinates was homogeneous.

The role of artificial sleep in the treatment of vasomotor rhinitis was studied on 25 patients by Efremova[6]. Artificial sleep therapy was considered effective in 8 patients, although slight recurrences took place. In 15 patients on whom 2% nicotonic acid and 40% glucose were also used, the combined therapy resulted in disappearance of

symptoms of vasomotor rhinitis. No recurrences ensued.

Popova and Kudrina[24] employed adiotherapy on 120 patients with acute and chronic sinusitis. The daily dose was 100 r with total therapy amounting to 300 r over a period of three applications every other day. Effective clinical responses were obtained in acute and subacute sinusitis. radiotherapy cured hyperplastic sinusitis, while in suppurative sinusitis, radiotherapy used in conjunction with irrigation and penicillin instillations into the sinuses proved very effective.

Scherbatoff[27] describes experiences with cholesteatoma of the maxillary sinuses in 36 patients. The ethmoid cells were also involved in 12 patients, and the frontal sinuses in 3 patients. Diseased teeth were considered the chief cause of the cholesteatoma.

Zimont[44] asserts that ligation of the dorsalis nasi (external nasal) arteries will relieve pain and retard the growth of malignant tumors invading the nasal cavity and the paranasal sinuses. In 69 patients thus treated, 7 were cured for periods ranging from 3 to 7 years, a response, according to the author, much better than when this form of intervention was not employed. Zjolnin[45] treated 31 patients with ozena, 23 of whom were women, by means of submucous implantation of preserved amnion and by Novocaine block of the postganglionic fibers of the upper sympathetic nerve chain. Good responses were obtained in 23 of these patients. Malkhazova[16] treated a group of patients with ozena at the Oto-laryngological Clinic of the Leningrad Sanitary Hygienic Institute, utilizing suppositories of chlorophylcarotine paste. This preparation was prepared from pine needles and contained vitamins, bitters, and balsamic substances. The intranasal odor disappeared for 2 days following introduction of the suppositories in the nasal passages. Repeated administration of the chlorophylcarotine paste caused deodorization for periods up to 5 or 6 days.

Twenty-five patients with rhinoscleroma were successfully treated by Evstafyeff[7] who used intravenous injections of embichin (a derivative of chlorethylamin) in amounts of 2 to 4 mg. The preparation was employed every other day until a total of 100 mg. was consumed. Shvartsberg and associates[31] found that 9 patients with rhinoscleroma could be effectively treated with intramuscular injections of streptomycin, 150 mg. being administered every 12 hours. Reduction and sometimes disappearance of the specific lesion were detected after 10 to 20 days of therapy.

A study by Boyko[2] showed that the temperature of the surface of the tonsils fell by 0.5 to 1.0 degrees Centigrade when the skin of the arm was cooled 3 to 4 degrees Centigrade. This was most marked in patients with vasomotor rhinitis. Cytological examination revealed a decrease in the number of phagocytes. In some instances, lowering of the temperature was followed by a rise in tonsillar temperature.

Yakovleva[42] tested the taste threshold in 40 patients who had tumors of the eighth nerve. Taste changes, which occurred in 35 patients, were mostly observed on the anterior two-thirds of the tongue on the side of the lesion, and depended on the stage and direction of the tumor growth.

Kolesov[13] investigated the amount of calcium, inorganic phosphate and magnesium in the blood serum and saliva of patients with tartar and salivary calculi. A pronounced increase in the calcium and phosphate contents was noted. The author believes these findings favor the theory that calculus formation is an expression of metabolic

disturbance. The structure of a calculus rests on the amount of mineral and amorphous contents.

In a protozoological study of the surgically removed tonsils of 72 adult patients, amebas (*Entamoeba gingivalis*, Gross, 1849) were observed by Toomka[38] in 4 patients and trichomonads (*Trichomonas elongata*, Steinberg, 1862) in 8 patients. The amebas in the tonsillar structures differed from those found in the oral cavity because of their larger size. This difference did not occur in patients in whom trichomonads were found. Amebas and trichomonads were present in the tonsillar lacunae but not in deep tonsillar tissue. Shukuryan[30] studied 250 cases of vivax and falciparum malaria in Armenia and observed that patients with malaria frequently develop tonsillitis and pharyngitis at specific times during the malarial attack. Acute nasal inflammatory episodes were also seen. Malarial relapses were associated with chronic nasopharyngeal infections.

Pliner[21] found the tongue affected in 4 of 17 patients who had actinomycosis of the cervicofacial area. The course of the disease was acute in one patient, while in 3 patients it lasted from 9 months to 5 years. Drainage and the administration of penicillin and actinolysate produced favorable clinical responses.

Braylovskiy[3] used diethylstilbestrol to treat 461 patients with acute tonsillitis. The dosage was one tablet (1 mg.) daily, administered on an empty stomach. Children 9 to 12 years of age received half the dosage. The clinical rsponse was considered impressive in 449 patients. Under this regimen, the attack of tonsillitis lasted 3 days and complications were rare. Khakkam[12] employed Roentgen irradiation on 243 patients with chronic tonsillitis and 121 patients with acute tonsillitis. Five years later an investigation demonstrated that no recurrences of the disease ensued in 23% of the patients irradiated during the acute attack of tonsillitis and none in 66% of the patients with chronic tonsillitis.

According to Misevitch[19], 6 patients with agranulocytic angina were successfully treated by means of pentoxyl, a derivative of nucleic acid.

Kozlova[14] injected Novocaine and alcohol-Novocaine solutions into the pharyngeal mucous membranes of 180 patients with chronic pharyngitis and chronic tonsillitis. Recovery took place in 29% of the entire group, with subsequent recurrence of the diseases in 11% of the patients. Improvement occurred in 52% of the patients, with recurrences in 2%. In 6% of the patients under observation, no changes occurred. There were no complications.

Tikhomirova[37] reported finding an incidence of 7.9% (549 patients) hemorrhage occurring postoperatively in a group of 6,937 patients who had undergone tonsillectomy. Hemorrhage usually occurred on the fifth postoperative day. Umanskiy[39] states that sulfathiazole is readily absorbed by the upper respiratory tract following inhalation in the treatment of patients with acute and chronic tonsillitis. One hundred and eleven patients, 5 to 60 years of age, were observed, and the response was most favorable in acute cases. Vengerovskiy[40] calls attention to the effect of hypnosis on 14 patients, aged 14 to 28, who underwent speech training. These patients started to stutter after sustaining psychotrauma during youth. Complete cessation of stuttering occurred in 8 patients, and improvement took place in the remainder.

In a group of 104 patients afflicted with syringomyelia, Melerovich and Lyande[17] detected 36 patients displaying involvement of the laryngeal muscles. Unilateral paralysis was observed mostly, often during the initial sta-

of the disease. No regularity was noted in the sequence of involvement of individual laryngeal muscles. Frequently, total unilateral paralysis of the larynx was well compensated. In cases of spinal gliosis, this was often the only symptom of syringobulbia.

A smear or scraping of a malignant pharyngeal or laryngeal tumor was stained with a 1:10,000 fluorochrome solution without fixation and examined microscopically in blue light by Gutkina[10]. Luminescence differed in healthy, damaged and necrotic cells, healthy epithelial cells appearing green, keratinized necrotic cells red. Light red, shining clubs of ribonucleinic acid are seen in cancerous cells. The method is easy to perform and was used on 49 laryngeal and 5 pharyngeal cancer patients.

Smutneva[33] treated 19 patients with papillomatosis of the larynx, using extract of chlidonium majus in combination with surgery. Nine patients thus treated recovered fully, 8 improved, and 2 were not benfited. Scherbatov[28] cites observations on 10 patients with laryngocele-type cysts of the larynx, 6 of which were external and 4 internal. A tendency toward inflammation of the wall of the cyst occurred, and this was believed frequently responsible for the absence of air in the cyst due to the obliteration of the duct.

Podgayetskiy[22] successfully treated 2 female children, aged 3 and 12, who had laryngeal stenosis of syphilitic origin with intramuscular injections of streptomycin. The larynges of 20 patients who died within 3 to 5 weeks after the onset of typhoid fever were examined by Tagayevskaya[34]. No clinical changes in the larynges had been observed before death. Necropsy revealed an absence of laryngeal lesions in 5 patients; the presence of hyperplasia of the lymphoid tissue in 5 patients; catarrhal laryngitis in 5 patients, and chondro-perichondritis in 5 patients.

Okooloff[20] described the findings in 80 patients, with pulmonary tuberculosis, who had been examined by indirect laryngoscopy and stroboscopy, 35 of whom died. Laryngoscopic and stroboscopic findings in 12 patients were normal, and this was confirmed at necropsy. Necropsy revealed tuberculosis of the larynx in 9 of 11 patients in whom laryngoscopic findings were normal but stroboscopy had demonstrated the true vocal cords to be affected. In 12 patients, necropsy confirmed the abnormal laryngoscopic and stroboscopic findings present while the patients were alive.

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SUMMARIO IN INTERLINGUA

(See page 447 for original article)

Mononucleosis Infectiose

Analyse De 100 Casos, Con Attention Special Prestate Al Diagnose, Al Tests De Function Hepatic, E Al Tractamento—In Casos Seligite—Con Prednisona

Le diagnose de mononucleosis infectiose es un thema controverse depost plus que 35 annos. Le differentias de opinion concerne principalmente le significa-tion e le interpretation del alterationes hematologic e del test de agglutination de cellulas ovin (*i.e.* a anticorpore heterophile). Un varietate de manifestationes clinic se trova describite in le litteratura, generalmente in consequentia del supra-mentionate differentias de opinion. Iste discrepantias es describite, con accentuation del notion que le accuratia diagnostic es cosa relative, dependente non de un sol aspecto specific del morbo sed del interrelation de varie factores de natura clinic e laboratorial. Criterios practic pro le diagnose es suggerite.

Es presentate un analyse de 100 casos, con respecto al datos clinic, al diagnose, al tractamento, al duration del morbo, e al complicationes. Le analyse indica le existentia de un grado satisfacente de congruitate del constatationes clinic e laboratorial in iste serie de casos.

Es discutite le divergente reportos de varie investigatores con respecto a altera-tiones hepatic. Es presentate datos que pare indicar (1) que alterationes functional del hepate es satis commun, (2) que le usual hepatitis de mononucleo-sis infectiose differe in su characteristicas ab lo que es generalmente trovate in hepatitis infectiose e hepatitis seral.

Le tractamento es generalmente symptomatic e supportative. Prolongate periodos de allectamento es usualmente necessari. Un micre gruppo de 17 patientes seligite esseva tractate con prednisona oral. Il pareva que isto initiava un prompte melioration symptomatic, specialmente un reduction del pharyngitis. Le hormon non obscurava le importante signos laboratorial, sed il es etiam notar que illo non pareva reducer le duration del morbo. Le ultime valor de therapia steroide in iste morbo remane a demonstrar.

Il es le complicationes de mononucleosis infectiose le quales—insimul con inade-quate discrimination diagnostic—ha generate le reputation de multiformitate pro iste morbo.

DERMATOLOGY AND SYPHILOLOGY

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DERMATOSES OF PREGNANCY
A REVIEW OF SOME OF THE RECENT LITERATURE

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IN the daily practice of the dermatologist, the internist and the obstetrician-gynecologist, a number of cutaneous and mucous membrane diseases of women are frequently encountered. The relationship between the gynecologic and cutaneous processes is so close that one may classify many of the associations as the gynecodermatologic diseases. In addition, in some of the physiologic phases occurring throughout a woman's life span, ordinary cutaneous processes and diseases are significantly modified. Furthermore, there are some dermatoses more prevalant in women, as well as a few serious dermatological diseases practically restricted to the female sex. It would require a textbook to discuss even superficially these gynecodermatologic diseases. Therefore, this communication emphasizes only those dermatoses associated with and which seem to be modified by or related to pregnancy. The hormonal changes in pregnancy no doubt are mainly responsible for most of these changes. For example, pituitary changes during pregnancy may account for certain growth and pigment changes of the skin and its appendages, increased thyroid activity may be responsible for certain sensations of heat, erythema and increased sweating, and increased adrenal corti-

cal activity may be responsible for the edema and striae of the skin during pregnancy. It should be emphasized that these glandular changes are not the only factors involved, but that the final picture is the result of the combination of a number of factors including endocrine, genetic and environmental. It should not be surprising that many of the cutaneous processes occurring during pregnancy may show such marked variations from the usual picture that it is impossible to classify them properly.

There are many good articles dealing with the dermatoses of pregnancy. A few of them are those of Hollander and Vogel[37]; Crawford and Leeper[20]; Russell and Thorne[63]; Ellis and Beresto[28]; Bean[8] and Greenberg, Pelliteria, and Barton[35]. Hollander and Vogel[37] classified the cutaneous and mucous membrane diseases associated with pregnancy into three groups: 1) Skin diseases precipitated by pregnancy; 2) skin diseases aggravated by pregnancy; 3) skin diseases benefited by pregnancy. Vleugels-Schutter[79] lists the following among the cutaneous affections seen during pregnancy: prurigo gestationis, herpes gestationis, and impetigo herpetiformis. These are considered by some authors as varieties of prurigo, dermatitis herpetiformis, and psoriasis respectively. This interpretation is not always supported by clinical evidence. Distortion of clinical pictures, considerable changes from the prototypes of the dermatoses, also occur in association with cutaneous affections of old age or in patients with diseases such as leukemia, Hodgkin's diseases, diabetes, and others. Other cutaneous processes may occur in pregnancy which show such marked variations that are unclassifiable or must be regarded as distinctive diseases.

Since Hollander and Vogel's[37] classification is generally practical, it is acceptable to us. We are particularly interested in the diseases comprising group one which includes pigmentary changes, impetigo herpetiformis, adventitous changes of the gingivae, molluscum fibrosum gravidarum, erythema of the palms and prurigo gestationis of Besnier. These will be considered along with processes of somewhat related character. Although Hollander and Vogel[37] did not consider herpes gestationis a disorder precipitated by pregnancy, it was definitely felt by Crawford and Leeper[20] that herpes gestationis is confined to pregnant women. In their investigation of 50,000 pregnancies, it was shown that dermatoses had but a low incidence (0.37%) in association with pregnancy and thus were not more frequent than in the general population. Herpes gestationis was the only dermatosis met exclusively in association with pregnancy. It is believed that pregnancy, hormonal changes and decidual necrosis may play a role in producing this dermatosis. Erythema multiforme, herpes simplex, herpes gestationis and drug eruptions were all more frequent in patients with toxemia of pregnancy. It is our opinion that herpes gestationis is a disorder precipitated by the pregnant state.

PIGMENTARY CHANGES. A definite increase in melanin pigmentation of the skin is observed during pregnancy. The pigmentation increases as pregnancy progresses and tends to diminish somewhat after pregnancy. There is an increase of the normally pigmented areas, that is, the genitalia, areolae of breasts, axillae, umbilicus and the linea alba. Occasionally, hyperpigmentation occurs in localized patches on the face and neck and is termed chloasma. The hyperpigmentation of pregnancy has been shown to be due to the increased quantity of melanocyte stimulating hormone produced by preg

nant women. Shizume and Lerner[68] using quantitative assays demonstrated that during pregnancy the melanocyte stimulating hormone was elevated at the end of the second month and continued to increase until term. Following delivery, there was rapid return to normal in a few days. Deutsch and Mescon[24] studied the melanocyte stimulating hormone excretion in a series of pregnant women during and for a short time after pregnancy. An increase in the melanocyte stimulating hormone excretion occurred after the second month and a sudden decrease occurred after delivery. These findings occurred in all patients who had normal uncomplicated pregnancies. One patient with toxemia of pregnancy had an elevated melanocyte stimulating hormone excretion postpartum. It is felt that this increased quantity of melanocyte stimulating hormone is at least partially responsible for this hyperpigmentation. In addition, progesterone has a direct melanocyte stimulating hormone-like action. The sex hormones may promote pigmentation in a number of ways. It is interesting that eunuchs tan poorly when exposed to ultraviolet light unless they are also given male sex hormones. The melanocyte stimulating hormone and pregesterone are not the only hormones connected with hyperpigmentation. Ito[41], in a recent report, showed that estrogen and pregnanediol were increased in pregnancy and in patients with chloasma and Riehl's melanosis, the increment being much higher in the former than in the two latter diseases. The increased concentrations of these hormones during the menstrual cycle tended to be higher in women with chloasma and Riehl's melanosis than in a normal nonpregnant woman. Consequently, these hormones are presumed to participate in melanin formation during pregnancy and in the diseases related to pregnancy. No abnormalities were observed in the urinary content of these hormones in cases of complete albinism. Chloasma refers to localized or generalized hyperpigmented patches. The increased pigmentation is invariably due to increases of melanin[9]. When these patches are small and well defined, they are often referred to by the laity as "liver spots." The color varies from hardly perceptible, to deep yellow, yellow green, chocolate brown or black shades. Chloasma occurring during pregnancy is termed chloasma uterinum. Pigmentation associated with pregnancy may clear after delivery.

The pigmentation of scars during pregnancy was studied by Teichner[74]. Scars resulting from operations or accidents which precede pregnancy by at least one year do not show changes during pregnancy. They may even become lighter than the adjacent normal skin. Scars which developed only a few months before, at the onset, or during pregnancy, will exhibit deep pigmentation similar to that observed in the nipples and in the linea alba. The closer the operation or injury is to the beginning of the pregnancy, the more marked is the pigmentation of the scar tissue. These observations were made on 71 pregnant women, 26 of whom had recent scars on various parts of the body. The possible mechanism of this phenomenon probably involves the melanotropic hormone and Vitamins A and C. Teichner[74] fails to state, however, whether there was regression of the hyperpigmentation after pregnancy.

PREGNANCY AND PORPHYRIA. Pregnancy and porphyria was recently reviewed by Vine, Shaffer, Pauley and Margolis[78]. They reported on 27 pregnancies in 16 women with porphyria. The porphyria was either of the acute intermittent or mixed type. From the

data in this review there was a decided tendency for the porphyria to exacerbate during pregnancy. The cause of the exacerbation of the clinical manifestations of porphyria during pregnancy was undetermined. It was suggested that the use of sedative drugs in early pregnancy may have been responsible, and although this may apply to certain isolated cases, it did not explain the phenomenon in the entire group. It was also apparent that therapeutic abortion was as detrimental as the pregnancy itself, and, therefore, cannot be recommended. In those pregnancies going to term the infants were as normal at birth as would be expected in the general population.

IMPETIGO HERPETIFORMIS. Although it has been seen in the nonpregnant woman and in a few instances even in man, impetigo herpetiformis, a rare but serious dermatosis, usually occurs in pregnant women. It is an inflammatory dermatosis characterized by groups of small pustules which at first appear as discrete lesions on the inner surfaces of the thighs and on the genitocrural areas. Each lesion is surrounded by an inflammatory halo. After a few days the pustules dry and the area becomes crusted at about the same time new lesions are forming in the periphery of the crusted areas, and slowly and relentlessly the disease progresses to become generalized. The same process involves the mucosa, especially the oral mucosa where the appearance because of the moisture is modified so that they resemble superficial greyish white erosions. The mucous membrane lesions are tender and painful and interfere with the patient's nutrition. On the cutaneous surface the lesions cause burning, pain and moderately severe pruritus. Systemic symptoms become grave as the disease progresses resulting in high fever, chills, vomiting and diarrhea, delirium and tetany. There is a rapid loss of weight and strength and in a majority of cases this serious disease terminates fatally. Clinically this disease must be differentiated from dermatitis herpetiformis, erythema multiforme and pemphigus vulgaris and this can usually be done if the clinical course is kept in mind and certain laboratory tests are performed, namely, Tzanck smear and biopsy of an early lesion. Unfortunately, the cause of impetigo herpetiformis is unknown. Therefore, therapy is empiric. Certainly broad spectrum antibiotics are indicated, and steroids should be tried. General supportive and local dermatologic measures are mandatory. Tenlén[75] described a patient with impetigo herpetiformis in pregnancy from 1933 to 1936; three outbreaks, each time in connection with pregnancy and successfully treated with hormones.

HERPES GESTATIONIS. Herpes gestationis is a rare disorder occurring during pregnancy or the puerperium. It is considered by Madden[53] as the second most frequent dermatosis of pregnancy. Although herpes gestationis is, at times, extremely disabling, as a rule it is not fatal. The disorder usually begins with pruritus followed by groups of small erythematous papules and vesicles located on the buttocks, legs, back, abdomen and forearms. Herpes gestationis usually begins during the second half of pregnancy and exacerbates and remits until the time of delivery or shortly thereafter when it completely disappears. In some women it recurs with each pregnancy. Duhring believed that herpes gestationis belonged in the dermatitis herpetiformis group. Eyster and Kierland[30] who studied 381 patients with dermatitis herpetiformis found that this disease occurs three times more frequently in males, and that pre-existing dermatitis herpetiformis may subside during pregnancy

only to recur thereafter. It is suggested by Pillsbury, Shelley and Kligman[59] and by Cawley, Wheeler and Wilhite[16] that in some cases herpes gestationis may be a cutaneous manifestation of incompatible Rh factors; since in many women with herpes gestationis pregnancy results in abortions, stillbirths or infants with erythroblastosis fetalis. In a recent review of herpes gestationis by Russell and Thorne[63] the following provocative conclusions were presented:

"1. If dermatitis herpetiformis is a specific disease, then herpes gestationis appears to be a separate disease entity. Herpes gestationis is much more consistent than dermatitis herpetiformis in its behaviour. 2. If dermatitis herpetiformis is a reaction—a 'morphological clinical syndrome' (Blaschko[11], 1889; Downing[26], 1945; Schultze-Frentzel[67], 1955)—then herpes gestationis can be regarded as a well-defined variant. 3. The exciting causes of herpes gestationis appears to be an abnormal metabolic or endocrine product of pregnancy, the puerperium and the premenstrual phase. The natural history suggests either that sensitization develops to this agent or that the agent is produced in excess, is incompletely destroyed, or is inadequately excreted. Increased gonadotropins found in blood and urine are unlikely to be of chorionic origin but may be of pituitary origin. 4. Cortisone is today the best drug for controlling herpes gestationis, and is safe for mother and infant, provided its use is limited to the second trimester and the earlier part of the third trimester. Prednisone should prove even more useful."

PEMPHIGUS ASSOCIATED WITH PREGNANCY. Pemphigus in association with pregnancy is exceedingly rare. Ten cases of pemphigus complicated by pregnancy and one case in which pemphigus occurred prior to conception have been reported in the literature. The latter case reported by Samitz, Greenberg and Coletti[64] is especially interesting from the endocrinologic standpoint. The dermatosis varied in severity during the three trimesters, a beneficial effect was noted in the first and third trimesters, and this is explained on the basis of rise in output of the endogeneous adrenal cortical hormones during these periods. In addition, the patient was treated with the steroid group of drugs and delivered of a healthy premature infant. Of dermatological interest is the fact that both mother and child survived and that the picture of pemphigus changed from the vulgaris to the foliaceous type.

STEVENS-JOHNSON SYNDROME IN PREGNANCY. Stevens-Johnson Syndrome has created considerable interest in dermatologic circles. We will not discuss here its nosology but will report on recent contributions in the field under discussion.

About one-fourth of the well over 100 cases of Stevens-Johnson Syndrome reported in the literature were in female patients[52]. In only 7 of these was there vulval or vaginal involvement, or both[1,21,31,39]. The vaginal lesions are similar to those involving the mouth, pharynx and lips. They are vesicles or bullae on an erythematous base and ulcerate rapidly. In one patient there was coalescence of the lesions and on healing, obliteration of the vagina. Ashby and Lazar[7], in an excellent review of the subject, have summarized the salient features of the disease. They describe prodromes of malaise, fever, and sore throat. Stomatitis is seen in every case. Over half of the cases reported in males showed penile lesions. The cutaneous lesions are multiform, erythematous, vesicular, and bullous. There is pulmonary involvement in about one-third of the cases. The mortality rate in Ashby and Lazar's[7] 77 collected cases was 10%. The cause of Stevens-Johnson Syndrome is unknown. The consensus is that it is allergic in nature. In many of the reported cases, its onset follows penicillin or sulfonamide therapy, but these

drugs may have been administered to treat the prodromes of the already existing disease and hence were probably not causative. Recently, adrenocorticotrophic hormone and cortisone have yielded good results[3,80]. Stevens-Johnson Syndrome has not been mentioned in the literature among the factors producing vaginal atresia. Caustic douches, trauma, and infections, specifically typhoid fever, diphtheria, and smallpox, are most commonly cited as causative. The management of atresia of the vagina complicating pregnancy has been outlined by Piklamaa[58]. He does not believe that the atresia should be treated during pregnancy because of the hyperemia that is present and also because of the danger of infection. If a thin membrane is present, it should be incised at delivery, but if the obliteration is more extensive, he advises Cesarean section with drainage of the uterus through the abdomen. In his case the vaginal obliteration was unrecognized until full cervical dilatation, because of the severe orthopnea necessitating the maintenance of high Fowler position and also because of the presence of extensive cutaneous lesions. Delivery by Cesarean section could not be considered and, therefore, immediate delivery was performed.

CHANGES OF THE GINGIVAE. Hollander and Vogel[37] in their paper have a thorough and complete description of this problem, and we therefore quote:

"During pregnancy certain structures of the oral cavity appear to be adversely affected. Dental caries, odontitis, and proliferative changes of the gingivae are among those conditions considered by some attributable to it. Full agreement, however, does not exist in this regard. The adventitious changes of the gingivae are acceptable as adventitious changes of pregnancy, but dental caries and odontitis have been made a controversial issue. A variety of titles have been employed to call attention to these changes. These titles include stomatitis gravidarum, gingivitis gravidarum, proliferative gingivitis of pregnancy, hypertrophic gingivitis of pregnancy, epulis gravidarum, and pregnancy tumor. These manifestations are of the same process, varying only in the degree of intensity of their reaction. The most common adventitious change is the occurrence of a marginal gingivitis. Generally, the lower teeth are most frequently and most severely involved. The disturbance makes its appearance at about the fourth month of pregnancy, usually when the mammary changes become evident. At first the gingivae are merely somewhat edematous, but soon hyperemia causes more extensive changes, adding color changes to the swelling. The gum margins become progressively darker red in hue until a dark bluish-red tinge is attained. The scurvylike similarity is accentuated by the ease of bleeding, which occurs either spontaneously or as the result of minor injury. This type of gingivitis, frequently spoken of as gingivitis gravidarum, persists throughout pregnancy and lasts one or two months after delivery. Under the title of pregnancy tumor or epulis gravidarum, a hemorrhagic proliferative change arising from the interdental gingival structures has been noted by a number of observers. This tumefaction is indistinguishable from the entity known as epulis, both in its clinical appearance and in its architecture definable by microscopic examination. Dark red, oval or rounded, easily bleeding tumefactions appear in pregnant women past the third month and these continue to enlarge while pregnancy lasts. They recede shortly after parturition. It has been noted that women showing these proliferative tumefactive changes of the gum margins have recurrences of the same difficulty in subsequent pregnancies. Even such radical procedures as electrodesiccation or excision of the tumors during pregnancy failed in instances to halt the appearance of proliferative gum changes, while spontaneous recession after parturition is the rule. Such a pregnancy tumor occurred in a 29-year-old woman who was in the seventh month of her pregnancy. In the fourth month of her pregnancy, she noted a bluish-red nodule protruding on the lingual side between the right lower lateral incisor and bicuspid. The tumor was friable and bled readily. A section taken from the affected area proved it to consist of granulation tissue. The tumor disappeared spontaneously at the termination of pregnancy."

MOLLUSCUM FIBROSUM GRAVIDARUM. Molluscum fibrosum gravidarum may be defined as a type of soft fibroma which develops during pregnancy. In some cases the soft tumors partially or completely disappear after labor but usually they persist and grow worse with each succeeding pregnancy. As a rule these are small pinhead to pea-size pedunculated tags occurring in the mammary region, sides and front of the neck.

VASCULAR CHANGES OF THE SKIN IN PREGNANCY. Bean[8] and his co-workers present an interim analysis of data concerning the incidence, natural history, and fate of vascular spiders and palmar erythema as observed in 1,243 women in the obstetrical clinic of the Cincinnati General Hospital. Vascular spiders apparently were first noticed as benign complications of normal pregnancy by Corbett in 1914 and have been recorded by dermatologists at intervals since then. An early note on palmar erythema of pregnancy was published by Feldman in 1939. Nothing about such lesions has been found in the American textbooks on obstetrics which we have consulted. Vascular spiders have been found in about two-thirds of the white women and 11% of the Negro women during pregnancy. They tend to appear in the early months of pregnancy, especially during the second through the fifth months. They increase slowly in number and in size until term, or shortly before. About three-quarters of them have faded by the seventh week after delivery. Details of vascular spider of pregnancy have been presented in photographs of the involved skin before and after delivery and demonstrate the rapid return to normal. Almost two-thirds of the white women and slightly more than one-third of the Negresses were observed to have palmar erythema during pregnancy. The appearance and the fading were more abrupt than with vascular spiders but the trends of the appearance and disappearance were similar. While the difference in incidence of the cutaneous vascular changes in white and Negro women was large, it is suggested that other factors than skin pigment alone may be involved. The depth of skin color is a major consideration. Vascular spiders and palmar erythema have not been reported in Negroes during pregnancy heretofore. Tests of liver function did not reveal significant abnormality, or differences between those with and without spider, or palmar erythema. There was no marked difference in incidence or number of vascular spiders or of palmar erythema between subjects who later developed toxemia and those who escaped it. According to Bean[8] and his group, the vascular spider of pregnancy presents no basic differences from those found in chronic liver disease. But, they are apt to be larger and more numerous in persons with cirrhosis than in pregnant women. These investigators have advanced the hypothesis that vascular spiders and palmar erythema develop as a response to the stimulus of high levels of estrogenic substances circulating in the blood for long periods.

PRURITUS IN PREGNANCY. Pruritus is a subjective symptom and not a disease; this symptom may arise from internal or external cause and may be localized or generalized. Abdominal pruritus in pregnancy may be caused by stretching of the abdomen during pregnancy. Kasdon[45] who studied 365 successive obstetrical patients calculated an incidence of 17.0% of uncomplicated abdominal pruritus during pregnancy sufficient to warrant complaint by the patient. In his study the incidence of this symptom appeared to be less during the first trimester than during the second or third

trimester. He concluded that this symptom was a local problem and in 9 out of 10 cases he reported complete disappearance of itching with the local use of antihistamine medicaments. Generalized pruritus of pregnancy, a different and more serious problem, was shown by Arfwedson[5] to be related to liver dysfunction. In his study, 65% of the cases of general pruritus of pregnancy showed an abnormal serum bilirubin as compared with 6% in the control group. Urobilinogenuria and bilirubinuria were 10 times more frequent among pregnant women with general pruritus than without. Toxemia of pregnancy was just as common in pruritic cases as in the nonpruritic cases, and that is 31% against 33%. Dietary measures consisting of fat poor, protein rich, high caloric diet with supplemental vitamins and medication with antihistamine agents and calcium complexes often gave relief and controlled liver and biliary dysfunction.

PRURITUS VULVAE OF PREGNANCY. Although pruritus vulvae occurring during the pregnant state may be caused by a variety of etiological agents, two major causes stand out: moniliasis and trichomonas vaginitis. Moniliasis occurring during pregnancy results in itching, burning and smarting of the vulva. In addition, there is thick, white and viscid leukorrhea. The vulva is red and swollen, while the vaginal mucosa is reddened and covered with greyish white placques. The diagnosis is easily confirmed by finding monilia in smears and cultures. As far as therapy is concerned, simple bland douches and the use of either 1% gentian violet, or nystatin intravaginally may control the infection[42,83]. Trichomonas vaginitis occurs especially during pregnancy and is often overlooked as a cause of local pruritus. The labia are excoriated and a copious bubbly yellowish discharge emanates from the vagina. The vaginal mucosa is greatly inflamed and in some cases the cervix will present typical multiple ecchymotic areas varying in size from 1 to 5 mm. These sometimes are called the "strawberry" cervices which are pathognomonic of trichomonas vaginitis. The diagnosis of trichomonas vaginitis is not difficult. The bubbly yellowish discharge is suggestive, and the positive diagnosis is made by finding the organisms in a hanging drop preparation. Trichomonas vaginitis may be treated with the use of vaginal suppositories of terramycin, and terramycin or atabrine by mouth.

PSORIASIS AND PREGNANCY. Nardelli[57] showed that between 45 and 50% of cases of psoriasis improved during pregnancy. No change was noted in psoriasis of the inveterate type limited to a few areas. Aggravation of psoriasis during pregnancy is indicative of the existence of some other pathologic process. The benefit during pregnancy is attributed to a flood of placental hormones.

LUPUS ERYTHEMATOSUS IN PREGNANCY. Ellis and Bereston[28] in 1952 reviewed the literature concerning this subject and in addition surveyed the opinions of 280 American dermatologists. From the data which they collected, the following conclusions were drawn.

"1. When accompanied by acute disseminated lupus erythematosus, pregnancy may result in 30% fetal mortality.

2. In acute lupus erythematosus the maternal mortality rate (25%) does not seem to be unduly influenced by pregnancy.

3. In pregnancy accompanied by subacute disseminated lupus erythematosus, there was 46% fetal mortality, but pregnancy with few exceptions, had little or no effect on the course of the disease in the mother.

4. In pregnancy accompanied by chronic discoid lupus erythematosus, no consistent effects on the mother o

child were noted." Friedman and Rutherford[32], who studied 188 cases of lupus erythematosus associated with pregnancy, summarized the effect of pregnancy on the course of lupus erythematosus as follows:

"The large majority of patients with the acute and subacute disseminated form experience notable subjective relief and occasional laboratory reversals as well. The basic disease process is not apparently specifically affected by the pregnancy, there being both exacerbations and remissions occurring in nearly equal numbers in early pregnancy. Of interest is the lack of change in the 3rd trimester. The disease resumes its prepregnancy status postpartum, usually within 2 months. Exacerbations are the rule, since so many become clinically quiescent during the pregnancy. Rapid progression of the disease process by pregnancy in patients in whom the disease was previously quiescent has been seen, but quite infrequently. This occurs in such small numbers that it may perhaps be explained as a chance occurrence, the pregnancy being an unrelated, superimposed incident. The question of therapeutic abortion is discussed and although insufficient data are available, it is implied that no real beneficial effect on the course of the disease may be expected from it. However, there was an increased incidence of abortions and premature births. The infants, if they are carried to viability, are apparently unaffected by the maternal disease."

Birth of a mentally retarded child by a mother afflicted with systemic lupus erythematosus and showing a possible false positive Kolmer test for syphilis has been reported[29]. The disappearance of the chronic types of lupus erythematosus during pregnancy and its recurrence after term has been observed by Michelson. (Ref. Symposium on Lupus Erythematosus Proc. Staff Meet., Mayo Clinic, **27**, 409, 1952.)

Although the use of hormonal therapy is not new in the treatment of acute lupus erythematosus[62], it has now been shown that prolonged remissions of lupus erythematosus can be produced with adrenocorticotropic and cortisone therapy[70]. It has also now been established that the steroid group of drugs may be used for therapy at any time during the pregnant state without fear of damage to the fetus[2,6,14,22,43,44,46,47,49,54,56,65,66,69]. Therefore, it is concluded that the steroid drugs, when indicated, should be used in treating systemic lupus erythematosus associated with pregnancy, regardless of the time of pregnancy and without fear of fetal damage.

LUPUS ERYTHEMATOSUS SIMULATING TOXEMIA OF PREGNANCY. Boyd, Stoddard and Pierce[12] discuss a case of acute systemic lupus erythematosus occurring as a rare complication of pregnancy, and stress the point that lupus erythematosus be considered in the differential diagnosis of all but the most typical cases of toxemia of pregnancy. Untreated lupus erythematosus during pregnancy often causes a grave prognosis for both the mother and the fetus, therefore, with early diagnosis and the proper use of the steroid group of drugs the lives of many young women will be prolonged.

SCLERODERMA AND PREGNANCY. Tischler, Zarowitz and Daichman[77] report a case of scleroderma in a 25-year-old woman occurring prior to pregnancy. The patient was treated with prednisone in moderate dosage for approximately 9 months prior to becoming pregnant. It is interesting that while receiving the prednisone, she not only became pregnant but carried through her pregnancy and had a normal spontaneous delivery. A normal healthy infant was born, and an uneventful puerperium ensued. The course of this patient's illness suggests that the prednisone had no effect upon her gonadal status, since she was maintained on 20 mg. of prednisone daily prior to becoming pregnant and menstruated regularly until pregnant. It should be noted that occasionally infants de-

livered of mothers receiving cortisone may show signs of reduced adrenal-cortex activity immediately postpartum.

DERMATOMYOSITIS ASSOCIATED WITH PREGNANCY. Glickman[33] reports an interesting case of a 27-year-old woman who, while being treated for dermatomyositis with adequate doses of Meticorten, became pregnant. During this pregnancy, the patient's condition definitely improved necessitating a lowered maintenance dose of Meticorten. After an uncomplicated pregnancy, the patient was delivered of a normal healthy full-term infant. The dose of Meticorten was increased immediately following delivery to prevent possible postpartum flare of the dermatomyositis. Glickman[33] suggests that the pregnancy had a beneficial effect on the course of the dermatomyositis, in this patient. Furthermore, adequate doses of steroids had no adverse effect on the patient's ability to conceive and evidentally this treatment did not interfere with the normal growth and development of the infant.

CANCER AND PREGNANCY. At the National Cancer Service in Brazil, clinical experience has created the impression that intercurrent pregnancy in a case of cancer aggravates the evolution of the tumor. Kroeff[48] reports a case of a 25-year-old patient developing a sarcoma of the anterior abdominal wall during her sixth month of pregnancy. She stated that in infancy she had an abscess at the same site which left a yellow-reddish nodule, and that this nodule had been traumatized repeatedly. This tumor was excised 2 months after delivery. A year later when she was 2-months pregnant, the patient was referred to the cancer center because the nodules had enlarged tremendously. At this time she presented a round ulcerated tumor, "the size of a fetal head" at the umbilical region. The tumor was diagnosed as a fibromyxosarcoma and removed. It recurred and was excised 4 more times with each pregnancy. The relationship between the tumor and the pregnancy became so evident to the patient that cicatricial pruritus constituted for her the best index of her pregnant state.

MALIGNANT MELANOMA. According to Byrd and McGarrity[15], malignant melanoma is probably a hormone sensitive tumor, as has been demonstrated experimentally with mouse melanoma. The spread of malignant melanoma is accelerated by the administration of testosterone to the mouse host[34]. The first evidence of hormone sensitivity is suggested by the 2 great classes of malignant melanoma: 1) Those occurring in the puberty period, and 2) those occurring after sexual maturation. The second group shows the greatest change from benign to malignant. The second clinical evidence lies in the change which moles and malignant melanomas undergo during pregnancy. Two patients with malignant melanoma were reported. The first demonstrated a recrudescence of the malignant melanoma with successive pregnancies and recession during the interim between pregnancies. While the tumor was obviously malignant, microscopically there was no evidence of regional or distant metastasis at the time of operation about 9 years after the first pregnancy. The second patient demonstrated the conversion of a junction nevus into a malignant melanoma during the second trimester of pregnancy. Adequate local excision was done at this time. The lesion recurred during a subsequent pregnancy, and in spite of the interruption of the pregnancy, the patient died.

The pigmentary changes associated with disease of the adrenal glands as in Addison's disease, pregnancy, and the administration of adrenocortico-

tropic hormone may be due to the increases in the blood of the adrenocorticotropic hormone. The increase in the adrenocorticotropic hormone in the circulating blood may be an important factor in melanocytic activity. The placenta has been shown to be an organ of formation of adrenocorticotropic hormone, and removal of the adrenal glands results in a marked increase of adrenocorticotropic hormone blood levels. If these observations are correct, the palliative procedure of choice for malignant melanoma is hypophysectomy as performed by Luft and Olivecrona[50]. As a result of the above facts, the following observations are suggested concerning the relationship of malignant melanoma to pregnancy:

1. Moles in pregnant females must be carefully watched, and those which are subject to irritation must be removed at the earliest possible moment.

2. All such removals should be accomplished in such a fashion as to permit microscopic examination without depending upon the so-called "critical eye" of the operator, but rather that of the microscopist.

3. All such removals must include a liberal margin of adjacent tissue to insure adequate local and initial removal of the lesion, for these tumors are notorious for local recurrence.

4. Should a malignant melanoma be found, appropriate local and regional node dissection should be carried out immediately and without regard to the state of the coexisting pregnancy.

5. The young woman who has had a malignant melanoma should be advised of the grave risk of pregnancy in that it may produce recrudescence of her tumor and appreciably shorten her life span. This risk is felt by the authors to be great enough to justify surgical sterilization on these women who are amenable to terminating their child-bearing career.

6. Castration has no value in the therapy or prevention of this neoplasm.

7. Termination of pregnancy before apparent spread has taken place may prevent or delay such spread. If metastases are present, there seems to be little value in premature interruption of pregnancy.

Sometimes there is spontaneous regression of malignant melanoma after pregnancy. For example, Allen[4] reports the case of a 38-year-old white woman who had a pigmented elevated lesion removed from the extensor surface of her forearm in 1942. In 1943, a black tumor appeared in the scar. This was resected widely and deeply. The specimen showed malignant melanoma histologically. In 1944, when the patient was 7-months pregnant, she developed multiple subcutaneous bluish nodules, "up to the size of marbles," on the left waist line, right flank, and right arm. These were regarded as blood-borne metastases and the prognosis considered hopeless. A lesion on the arm was removed for histologic examination and malignant melanoma was found. Two weeks after birth of a normal child, there were further deposits in the right scapular and inguinal areas. Approximately 2 months later, all nodules had disappeared except a small one in the right groin. The patient was feeling well and gaining weight. She was still well 12 years after excision of the primary lesion and 11 years after the appearance of the widely scattered metastatic lesions. In this case, the clinical and histological evidence pointed to a malignant melanoma recurring in a widely disseminated form during pregnancy and disappearing spontaneously after delivery. The sequence of events suggests that the metastases developed as a direct response to the stimulus of pregnancy and were so dependent on this stimulus that on its withdrawal they themselves disappeared.

LEUKEMIA AND PREGNANCY. The cause

of leukemia still remains unsolved, and there is no satisfactory evidence that the existence of pregnancy enters as an etiologic factor. Lutz[51] found 94 cases of leukemia and pregnancy in the literature. His case brings the total to 95. Thirty-nine of these were of the acute variety and 56 were chronic. Angelucci (1944), reporting a case, raised the question of reasons for the uncommon occurrence of pregnancy complicating leukemia, a disease which is responsible for 3,500 deaths yearly in the United States alone. In material from necropsies, marked leukemic infiltrations of the uterus, ovaries and tubes sufficient to interfere with conception has been reported. This was especially noted in the lymphatic type. Most of the cases of leukemia complicating pregnancy are of the myeloid type. Although secondary amenorrhea is infrequent in leukemia, more than one pregnancy has been observed in some patients with the chronic type of the disease. Leukemia has not been passed from mother to fetus probably because the placenta is a barrier to the passage of leukemia cells. No child born to a mother suffering from leukemia has developed leukemia, but congenital leukemia in children of nonleukemic mothers has been reported. A few cases of leukemia in the mother with onset after childbirth have also been reported. Acute leukemia usually has its onset after the pregnancy has been established. Most cases of leukemia occur in primipara. Pregnancy is believed to have little, if any, influence on the progress of the disease, and the presence of leukemia does not necessarily mean that the patient will fail to go to term. The maternal prognosis in acute leukemia is generally unfavorable, but the prognosis of chronic leukemia is somewhat better. Chronic myeloid leukemia is most frequent, especially in multipara. The lymphatic variety is rare in pregnant women.

Earlier studies on leukemia in pregnancy favored the interruption of pregnancy in acute leukemia but the consensus now is that nothing is gained by this procedure except in terminal cases where there is the possibility of saving a living child. In chronic leukemia, the chance of carrying the patient through the prenatal period and delivery is reasonably good. As mentioned previously, more than one pregnancy has occurred in mothers with chronic leukemia. The interruption of pregnancy in the chronic type also is believed to have no effect on the course of the disease.

Roentgen-ray therapy has definite merit in the treatment of chronic leukemia coexisting with pregnancy. Treatment to the spleen, with careful shielding of the remainder of the abdomen, is readily accomplished. Irradiation of the sternum, the dorsal spine, and the long bones may be given in addition to control the leukocyte count. Lutz[51] reports a case of chronic myeloid leukemia with coexisting pregnancy. The disease was controlled by small doses of Roentgen-ray therapy. This patient gave birth to a normal child. Her condition was further controlled by Roentgen-ray therapy for about 6 months postpartum, and controlled afterward by Urethane therapy, this patient being alive and symptomatically well one and one-half years after childbirth.

In a study based on 5 personal cases and a review of the literature, Harris[36] concluded that pregnancy is rare in patients with leukemia because of the poor condition of the patients, who almost always suffer from anemia, ammenorrhea and leukemic infiltration and destruction of the ovaries and endometrium. The maternal mortality in acute leukemia is 100%, while in chronic

leukemia, it is 36.5%. The fetal mortality in acute leukemia is 60%, while in the chronic type it is 16.4%. Harris[36] points out that abortion and premature labor are common in patients with acute leukemia, less so in chronic leukemia. The earlier, in the course of leukemia, pregnancy occurs the better the outlook for the mother and child. Although there is a marked hemorrhagic diathesis in leukemia, serious hemorrhages at the time of delivery, abortion or Cesarean section are not common. Adrenocorticotropic hormone, cortisone and aminopterin are of little value in the treatment of acute leukemia and produce only short remissions. Irradiation to the spleen has good results in chronic cases during pregnancy, no ill effects were noted in the child. Urethane and Fowler's solution are not contraindicated and seem to have a favorable effect on the child.

PREGNANCY AND HODGKIN'S DISEASE. Hodgkin's disease as a complication of pregnancy is uncommon. Three such cases were seen in the tumor clinic of the Boston Dispensary. From study of these cases, it was concluded that Hodgkin's disease does not grossly affect ovulation, fertility, incidence of spontaneous abortion, antepartum, intrapartum, or postpartum hemorrhage. Pregnancy does not seem to influence the course of Hodgkin's disease nor are the obstetrical aspects of gestation, parturition and the puerperium affected by coincidental occurrence. Three reports have appeared in the literature of infants with Hodgkin's disease who were born of mothers affected by this condition. The possibility of placental transmission of Hodgkin's disease must be remembered. From present evidence, interruption of pregnancy in patients afflicted by Hodgkin's disease is not indicated. Southam, Diamond, and Craver[72], of the Memorial Center for Cancer in New York City, also studied 59 patients with Hodgkin's disease associated with pregnancy. These 59 patients had 133 pregnancies, 50 of which were completed before the occurrence of the Hodgkin's disease, while the other 83 were concurrent with the disease. From their data it was suggested that Hodgkin's disease arising during pregnancy is detrimental to the prognosis of the patient, but whether or not therapeutic abortion would be beneficial could not be answered. They also studied the effect of Hodgkin's disease on the pregnancy and concluded that whenever there was evidence of disseminated disease, intra-abdominal disease, or active disease in any area, the incidence of spontaneous abortion was increased. A follow-up study of 21 children resulting from pregnancies occurring in mothers with Hodgkin's disease indicated that there were no additional disease risks to the offspring.

From 1921–1952, 373 patients with Hodgkin's disease, including 167 females, were treated at the Radiumhemmet in Stockholm by Hultberg[38]. One hundred of the women were between the ages 15 and 45, and 13 of these had one or more pregnancies and gave birth to 19 healthy children. In addition, there were 4 spontaneous and 3 induced abortions. In no case does pregnancy appear to have caused an acute exacerbation of the Hodgkin's disease. Eight of the patients are alive and in good health, 8 to 15 years after onset of the disease. None died in connection with pregnancy or within a year after delivery. Pregnancy, parturition and puerperium ran normal courses from the obstetric point of view. On the basis of the literature and Hultberg's[38] personal experience, the following conclusions were drawn:

"1. Pregnancy is not uncommon during the course of Hodgkin's disease.

2. From the obstetric point of view there is no reason to interrupt pregnancy in that disease; for pregnancy, parturition and puerperium run a normal course.

3. There is no evidence that exacerbations are more common during pregnancy than otherwise.

4. There is no conclusive proof that Hodgkin's disease may be transmitted from the mother to the child via the placenta; on the contrary, the great majority of children are healthy, and in some cases have been followed until adult age.

5. Only in a few exceptional cases is it justified to interrupt pregnancy in Hodgkin's disease; namely, where complicated by tuberculosis or some other disease or when the patient's general condition is so badly affected that death of the mother may be feared before full term, so that no possibility of saving the child can be expected, where the disease is localized to the inguinal or pelvic regions, making Roentgen treatment impossible for fear of the risk of radiation damage to the fetus, and where the mother has previously undergone treatment with nitrogen mustard or other radiomimetic substances.

6. Lactation may be permitted if the patient is in good condition and does not require radiation treatment; it should otherwise be withheld or for the sake of the child, possibly allowed tentatively for the first 2 to 3 weeks."

Bichel[10] believes that fertility is probably not affected by Hodgkin's disease since several women conceived more than once during the course of this disease. Bichel's[10] study was based on 57 women with Hodgkin's disease and entailed 65 pregnancies, 42 of which went to term. There were 3 stillborn deliveries, 3 premature births, and 12 spontaneous abortions. There were no cases of severe postpartum hemorrhage. Some cases of Hodgkin's disease were aggravated during pregnancy, especially in the postpartum state. These patients showed acceleration of the disease with rapid glandular enlargement and a fatal outcome after parturition. Since the course of Hodgkin's disease is erratic and exacerbations are frequent, all exacerbations in pregnancy, therefore, cannot be ascribed to the pregnancy itself. In some instances, no effect whatsoever was noted, either on the Hodgkin's disease or on the pregnancy. Hodgkin's disease seems to be less severe in women than in men and the possibility of the effect of female hormones upon this condition has been considered. Thus far, all the children resulting from pregnancy in women with Hodgkin's disease seem to be normal and healthy, but Bichel[10] states that an hereditary predisposition to Hodgkin's disease may be present. There was no evidence of Hodgkin's disease in aborted fetuses and placentas. The results of Bichel's[10] studies indicate that it is impossible to decide whether patients with Hodgkin's disease who have gone through a pregnancy will die earlier than they would without pregnancy. From the clinical standpoint, there seems to be no indication for interruption of pregnancy[76].

GERMAN MEASLES AND PREGNANCY. As so often happens in the field of medicine, it is now being demonstrated that early statistics and conclusions may need altering. In a recent and significant report by Greenberg, Pellitteri, and Barton[35], it is concluded that the incidence of congenital deformities among live-born babies of women with rubella during the first trimester of pregnancy was 9.7%. This is compared with a 7.0% incidence of congenital malformations of infants delivered of pregnant women who did not have rubella. From their data, they

will concede that there is an association between rubella early in pregnancy and the occurrence of congenital malformations in the offspring. Their calculated percentage is approximately 12% and when this is compared to previous rates of 90 to 100%, one realizes that further work is necessary to clarify this tremendous and important difference. They emphatically state that blanket advocacy of therapeutic abortion in pregnant women who developed rubella early in pregnancy is medically unjustified. They recommend as medically justified and as a sound public health procedure exposure of susceptible young girls to cases of rubella. Ingalls[40], who studied 100 cases of rubella during pregnancy, concluded that 20% of the offspring were stillborn or had serious congenital defects. He, too, recommends exposure of young girls to rubella. Along the same line, but somewhat more specific, is the report of Stuckey[73], who studied the incidence of congenital heart defects following maternal rubella during pregnancy. From a total of 426 patients with congenital heart disease, there were 44 with a history of maternal rubella during pregnancy, 27 of which were considered to have congenital cardiac defects. Thirteen had a patent ductus arteriosus, 4 a ventricular septal defect, 3 an atrial septal defect, 2 tetralogy of Fallot, and one each had aortic stenosis, pulmonary stenosis, coarctation of the aorta, the Eisenmenger complex, and transposition of the great vessels. The relative incidence of the various lesions agreed closely with that found in the general population, except that patent ductus arteriosus occurred about 8 times more frequently than the other congenital defects. He suggests as an explanation for this higher incidence the relatively much longer time of the critical period of the ductus arteriosus indicating a much longer time that this structure is at risk. With this in mind, the fact that patent ductus arteriosus does not predominate unduly over other congenital cardiac defects in the general population may suggest that genetic rather than environmental factors are responsible for the great bulk of cases of congenital heart disease (For further discussion see **Hill, A. B., Doll, R., Galloway, T. McL.,** and **Hughes, J. P. W.:** Brit. J. Prev. & Social Med., **12,** 1, 1958; **Dumont, M.:** Gynec. & Obst., **56,** 99, 1957; **Caronia, G.:** Boll. ocul., **35,** 593, 1956).

CONGENITAL VACCINIA AND VACCINIA GRAVIDARUM. Considering the countless millions of vaccinations that have been done, it is remarkable that congenital vaccinia has been described only once before (Lynch, 1932). In 1950 there was an outbreak of smallpox in the west of Scotland and many people requested vaccination. Among them was a young woman approximately 3-months pregnant who had never been vaccinated. She developed a severe primary reaction, and 3 months later she was delivered spontaneously of a feeble hydropic premature infant covered with severe generalized vaccinia. The child died 18 hours after birth. The recognition of this case prompted further investigation to determine the frequency with which vaccination during pregnancy has a harmful effect on the fetus[52]. The conclusions reached from this study are:

"1. Vaccination of a pregnant woman may, though rarely under special circumstances, lead to fatal generalized vaccinia of the fetus, and

2. Vaccination of a pregnant woman during the first trimester of pregnancy, significantly increases fetal mortality."

From these findings and those of Breniarz and Dabrowski[13], it is clear that vaccination should not be performed

during the first trimester of pregnancy as part of routine public protection and that it should be done at this stage of pregnancy only in women who have been in contact with smallpox. Damage to the fetus is produced, however, only during the first trimester of pregnancy, and there is virtually no risk from vaccination during the later months.

THE PATHOGENESIS OF POSTPARTUM PHLEBITIS. Puerperal phlebitis of infectious origin has become extremely rare since penicillin has been used routinely in all cases of suspected puerperal infections. However, another apparently noninfectious type of thrombophlebitis is frequently observed[71]. This form is characterized by sudden onset (between the eighth and twelfth day of the puerperium) normal lochia, absence of leukocytosis and negative blood cultures. An hereditary tendency toward phlebitis and placenta previa are the most important predisposing factors. It is possible that repeated small hemorrhages during the last trimester of pregnancy, as they occur in placenta previa, may increase the blood coagulation and so predispose to thrombophlebitis. Routine examination of the clotting time and sedimentation rate should be made at short intervals in all cases of placenta previa and in patients with a family or personal history of phlebitis. At the first sign of phlebitis, treatment with anticoagulants should be instituted. It is suggested that heparin be used in dosage of 75 mg. every 4 hours for 3 to 6 days. To replace heparin with Dicumarol after the first 24 hours is not advisable after delivery as the Dicumarol may cause uterine hemorrhage. Controls of the coagulation time during heparin therapy should not be repeated more often than once in 24 hours because of the danger of obstruction of veins needed for treatment. Hemorrhagic episodes occur infrequently with this suggested dosage. Hematuria is always the first sign of hyperheparinemia and indicates the need for immediate reduction in dosage. After the seventh day of the puerperium, Dicumarol ethyl acetate should be given orally beginning with 600 mg. every 6 hours for 3 days. It should then be reduced to 300 mg. every 12 hours on the seventh or ninth day. Prothrombin levels should be determined daily. Penicillin is completely ineffective in these patients.

AN UNUSUAL CASE OF BLASTOMYCOSIS OCCURRING DURING PREGNANCY. Wheeler and Cawley[81] report an unusual case of blastomycosis occurring in a 33-year-old white woman who was in her sixth month of pregnancy. The lesion occurred on the left side of her face, was chancriform in appearance, was associated with regional adenopathy and healed spontaneously. The diagnosis was confirmed by microscopic and cultural studies. The authors postulate that some agent or agents associated with pregnancy may be responsible for this beneficial effect. Pillsbury, Shelly and Kligman[60] would classify this as a case of primary cutaneous blastomycosis and would expect the lesion to follow the above described course, and therefore, they would not consider this an unusual case.

DISSEMINATED GRANULOMA INGUINALE AND ITS RELATIONSHIP TO GRANULOMA OF THE CERVIX AND PREGNANCY. Previous case reports of granuloma inguinale disseminated by the hematogenous route were reviewed by Cherney, Jones and Peete[17]. There were 8 women in this group. Seven of these had demonstrated cervical granulomas. In only one patient was it certain that pregnancy played no part in the dissemination of this disease. This was a 21-year-old Negress with disseminated granuloma inguinale which was treated

successfully with tetracycline. They consider this patient the first to be thus successfully treated. They recommend that 500 mg. of tetracycline be given intravenously twice a day for 3 days in such cases. Then 2.0 gm. orally daily to a total of 76.0 gm. are advised. In addition, they recommend a high protein diet with supplemental iron and vitamin therapy. Therapy should be continued for a short time after Donovan bodies disappear from the lesions.

SPONTANEOUS HEALING OF SICKLE CELL ANEMIA ULCER IN PREGNANCY. There is a difference of opinion concerning the effect of sickle cell anemia on the health of pregnant women. Cornbleet[19] reviewed this subject and reported the case of a 20-year-old Negress who was treated for sickle cell anemia and a large ulceration on the ankle. With systemic and local treatment for a period of 2½ years, the ulcer showed little progress toward healing. With her first pregnancy, the ulcer quickly and completely healed spontaneously, and in addition, the abdominal crises that she frequently experienced prior to pregnancy ceased. The pregnancy was uncomplicated and delivery was normal. Three months postpartum the ulcer reappeared, and in spite of diligent care, it soon reached its original size. There was no marked change in the sickling trait, hemoglobin, or erythrocyte count to explain the postpartum breakdown of the ulcer. This case suggested that sickle cell anemia was of no threat to this pregnancy. It should be noted, however, that this patient had close and detailed modern obstetrical care, a factor which undoubtedly contributed to the good result.

ALLERGIC DISEASES DURING PREGNANCY. The histamine inactivating property of the blood is four to thirty times more marked during pregnancy[27]. This power is demonstrated in the first months of pregnancy. It reaches a peak in the sixth and seventh months and diminishes slightly toward the end of pregnancy. This observation tends to refute the theory that allergic disease is aggravated and that latent allergy often becomes clinically manifest during pregnancy. The number of improvements in the allergic state during pregnancy was 6 times as high as the number of aggravations. Pregnancy has a favorable effect on hay fever, Quincke's edema, urticaria and vasomotor rhinitis. There was a considerable number that remained unchanged and a few that became aggravated. Allergic eczema and mucous colitis were not influenced by pregnancy.

VARIATIONS OF THICKNESS OF HAIR IN PREGNANCY. Because of previous findings of variation of thickness of the hair in dysmenorrheic women, Piredda[61] examined 20 Sardinian women in various stages of pregnancy. An important condition was that the hair did not receive any dyes, peroxide, or chemical waving. The requirements named make it difficult to duplicate the investigation in this country. The pre-pregnancy hair was compared with that during pregnancy. A marked enlargement was found at the beginning of pregnancy. The hair examined under polarized light showed no variation.

THE VARIATIONS IN SEBACEOUS SECRETION OF THE SKIN DURING PREGNANCY AND THE PUERPERIUM. Depaoli[23] found that there was no difference in the rate of sebaceous secretion during the last month of pregnancy and the first few days of the puerperium. Also, there was no difference in the rate of sebaceous regeneration during these 2 periods. Generally, the maximum values during pregnancy were higher than in puerperium.

PREGNANCY AND APOCRINE GLAND DISEASES: HIDRADENITIS, FOX-FORDYCE DIS-

EASE. Cornbleet[18] presented a woman with Fox-Fordyce disease and 2 with hidradenitis suppurativa who had remissions from their disease or were improved during the pregnant state. Following delivery, the disease relapsed in 2 of the patients. The third patient was lost from observation. From his histological studies, Cornbleet[18] suggests that the apocrine glands are less active and secrete less during the pregnant state. Since the apocrine glands are under hormonal control, it seems that some hormone or hormones connected with pregnancy are responsible for the amelioration of apocrine gland diseases during the pregnant state.

SARCOIDOSIS AND PREGNANCY. Mayock[55] and his group at the University of Pennsylvania studied 10 patients with sarcoidosis during the course of 16 pregnancies. Multiple manifestations of sarcoidosis were usually present, and in 8 of the 10 patients improvement of some of them occurred during the period of gestation. Except for the development of cutaneous lesions of the leg in one patient, no progression of the disease during pregnancy was noted. Relapse frequently occurred after delivery, and 4 patients developed new manifestations in the immediate postpartum period. There were 2 premature deliveries with one stillbirth, and 3 infants developed congenital abnormalities. These observations indicate that pregnancy usually has a beneficial effect on sarcoidosis. This is often lost after delivery.

WASSERMANN AND KAHN REACTIONS DURING PREGNANCY. Donnelly[25] was primarily interested in the age-old statement that pregnancy causes an increased incidence of positive serologic reactions to the tests for syphilis and that pregnancy exerts a beneficial effect on the course of syphilis. From his survey of the Scandinavian, English and American literature, he concluded that false positive reactions were no more frequent in pregnant women than in nonpregnant control group. He also contended that the false positive reactions which were noted in the pregnant women, as well as in the nonpregnant control group, are due to technical variations rather than some factor associated with pregnancy. The effect of the duration of pregnancy on biologic false reactions showed no significant variations so that the hormonal and physiologic changes apparently had little or no effect on the reaction.

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BOOK REVIEWS AND NOTICES

MANAGEMENT OF THE PATIENT WITH HEADACHE. By PERRY S. MACNEAL, M.D., Physician, Pennsylvania Hospital; BERNARD J. ALPERS, M.D., Sc.D.(MED.), Professor of Neurology, Jefferson Medical College and WILLIAM R. O'BRIEN, M.D., Psychiatrist, Pennsylvania Hospital. Pp. 145. Philadelphia: Lea & Febiger, 1957. Price, $3.50.

THIS monograph should be in every physician's library no matter in what type of practice he is engaged. The universal symptom is superbly considered from the standpoints of an internist, a neurologist and a psychiatrist. True there are some ideas with which some might not agree but the authors are outstanding authorities with a wealth of experience. It is a bit disturbing for instance to read that an idiopathic neuralgia such as tic douloureux may be characterized by objective sensory changes in the involved area. To the reviewer this would immediately rule out neuralgia as such.

It is refreshing to find that a psychiatrist speaks of his field as dealing "with things not with measurable quantities and it is, therefore, impossible to establish base lines or controls." This is so different from the dogmatism and absolute sureness one is apt to encounter. Also appreciated by the reviewer was the emphasis placed on the taking of an adequate, detailed, good history, a part of our care of patients so often slighted because of the pressure of too much work.

Consideration is given to organic, psychological and vascular mechanisms of head pain. Other chapters consider headache as a symptom of systemic disease, the differential diagnosis and treatment of head pain and diagnostic techniques. In the opinion of the reviewer the authors have accomplished their humble hope that this volume will help the practitioner. S. G.

ETUDE DE LA FONCTION THYROIDIENNE AVEC L'IODE RADIOACTIF. By PROF. A. VANNOTTI (Clinique médicale universitaire, Lausanne, Switzerland). Pp. 203; 41 ills. Basel, Switzerland: Benno Schwabe & Co., 1957 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $6.25.

THIS book is written by an authority in his field. The material is arranged as follows: one chapter deals with the normal function of the thyroid and with intermediate iodine metabolism; the next chapter, on alterations of thyroid function, deals first with the interrelationship of thyroid function with that of other endocrine glands, and then with the pathogenesis of malfunctions of the thyroid. This is followed by a chapter on new methods of study of thyroid function; it includes the use of I-131 and that of chemical determination of blood iodine. Next the clinical results obtained by I-131 tests in normal individuals and in cases of thyroid disease are discussed. The last chapter deals with results seen in secondary alterations of thyroid function. This brief enumeration of the chapter headings hardly conveys the amount of information packed into the 200 odd pages. This book will be especially valuable to the American clinician and clinical investigator. Whereas I-131 uptake, conversion ratio and the like do not differ as between the two sides of the Atlantic, clinical interpretations, being less mathematically precise, do differ, a fact that we are sometimes apt to forget. It is especially for this reason that I enjoyed this book based on a broad coverage of the literature as well as on the extensive observations of the author and his school. K. P.

BRAIN TUMORS: THEIR BIOLOGY AND PATHOLOGY. By K. J. ZÜLCH, M.D., Professor of Neurology, University of Cologne and Head, Department of General Neurology, Max Planck Institute for Brain Research. American Edition based on the Second German Edition; Translated by ALAN B. ROTHBALLER, M.D., M.SC. AND JERZY OLSZEWSKI, M.D., PH.D. Pp. 308; 84 ills. New York: Springer Publishing Company, Inc., 1957. Price, $9.50.

THIS is a translation of Zülch's second German edition on Brain Tumors by Rothballer and Olszewski. These two translators are to be congratulated for their clarity of expression. This is a relatively small book of 308 pages, but between its covers there is a wealth of material and information. Zülch backs up the majority of his statements with factual evidence and personal experience. While some of the material, such as the chordoma, is briefly covered, the salient features are adequately and concisely discussed. The first chapter deals with th

classification of brain tumors, including the historical development of the various classifications and the present state of classification, concluding with a classification by the author, which is based not only on cell origin and histological considerations, but also on biological activity. The author decries the changes of names of tumors without valid reason. There is an entire chapter devoted to the general statistical and biological data on brain tumors followed by the gross and microscopic appearance of these tumors in general. The ensuing chapters discuss the individual tumor groups and the individual tumors in these groups. A chapter on space-occupying processes that may be confused clinically and grossly with the neoplasms is also included. The concluding chapter takes up the methods of pathological study, including fixation, sectioning and staining. A bibliography of 42 pages completes the text. This is an authoritative book on brain tumors and is highly recommended by the reviewer. A. P.

TEXTBOOK OF GYNECOLOGY. By JOHN I. BREWER, B.S., M.D., PH.D., Professor of Obstetrics and Gynecology, Northwestern University Medical School, Chief of Gynecology and Obstetrics, Passavant Memorial Hospital, Chicago. 2nd ed. Pp. 742; 204 ills. Baltimore: The Williams & Wilkins Company, 1958. Price, $15.00.

The formal teaching of gynecology has traditionally consisted of a complete discussion of the disorders affecting each of the various genital tract structures. In many instances little attempt has been made to take advantage of the differential diagnostic problems encountered in gynecologic diseases. This method encourages the accumulation of unorganized facts which may not be particularly valuable to the student or the physician confronted with a patient with pelvic symptoms.

Brewer, in the Second Edition of his Textbook of Gynecology, has again attempted to present the material in a manner which is not only designed to make the student think in broad terms, but which makes the book a practical reference for the physician in practice. Part I is concerned with gynecologic signs and symptoms and Part II with more complete discussions of major entities such as pelvic inflammation, cancer, and others.

The material in Part I presents a sequential survey of gynecologic disorders during childhood, maturity and senescence. Much of this portion is directed toward differential diagnosis under headings such as: asymptomatic pelvic tumors, pelvic pain without tumor, pelvic pain with tumor, and the like. Under each heading the diagnostic features of appropriate lesions are presented. In addition, material such as endocrinology, leukorrhea, the climacteric, incontinence of urine, incontinence of feces, postmenopausal bleeding and other symptoms are similarly presented.

The text is well illustrated with clear black and white photographs of many of the lesions and of their microscopic anatomy.

The manner in which the material is presented makes a certain amount of repetition necessary, but as the author states ". . . repetition is good pedagogy . . ." Certainly if a student is familiar with the concepts of gynecology as they are detailed in this book he will have more practical information than many have had in the past. For the basic courses it might be a bit easier for the student if Parts I and II were transposed. He could thus first acquire a considerable amount of fundamental basic information which might enhance his ability to become proficient in its application.

This book should prove most helpful to the family physician, the intern and the young resident because he can find in it many helpful suggestions as to how to interpret his findings on pelvic examination and how to treat common gynecologic disorders. There is much in it, however, from which the mature gynecologist can profit. The directions are specific and are not clouded by prolonged discussions of theoretical, unproven or discarded theories and treatment regimens. An excellent bibliography is appended to each chapter. J. W.

THE MALABSORPTION SYNDROME. Edited by DAVID ADLERSBERG, M.D., The Mount Sinai Hospital. Pp. 252; 66 ills. New York and London: Grune & Stratton, Inc., 1957. Price, $5.50.

THIS monograph derives from a symposium held at the Mount Sinai Hospital. Dr. Adlersberg and his associates have had a long-standing interest in the absorptive problems of the small intestine particularly as they pertain to sprue, celiac disease, pancreatic disease, regional enteritis and following extensive small bowel resection. The investigative and clinical material presented is largely based upon experience with 94 patients affected by the malabsorption syn-

drome and, in addition, two chapters are included which have been written by well qualified British colleagues, W. Trevor Cooke and Margot Shiner. Physiology of absorption, abnormalities of metabolism, pathology of necropsy and biopsy material, clinical and Roentgen aspects of malabsorption as well as sections on blood, bone marrow, bone and neurological aspects of these disorders are all extremely well presented. The continuity evident in this book derives from the use of a single group of patients for most studies. The book is up-to-date, informative, provocative and highly recommended.

S. L.

THE BACTERIOLOGY OF TUBERCULOSIS. By EGONS DARZINS, M.D., Anoka, Minnesota, State Hospital. Pp. 488; 54 ills. Minneapolis: University of Minnesota Press, 1958. Price, $10.00.

FROM beginning to end this book is a thorough and unusually well written account of the tubercle bacillus. Each phase of the subject is handled chronologically, sometimes starting with historical gems as is the case with stains.

It could well serve as a textbook of tuberculobacteriology were such a thing needed, but it is really a reference book, and an exceedingly good one. Anyone who wants an up-to-date review of the cord factor, or any one of dozens of other topics, will find Darzins' discussion complete and, above all, very interesting, easy reading.

There are five sections: the cell itself; metabolism; methods for isolation and identification; types and pathogenicity; and experimental procedures. The high quality of the subject matter is maintained in the 88 pages of bibliography, and in author and subject indices. Finally, the publisher is to be congratulated for using a fine grade of paper, good binding, and an attractive format.

What Arnold Rich's "Pathogenesis of Tuberculosis" has meant to the phthisiologist, this book could mean to the bacteriologist. It is a MUST for all who are interested in the tubercle bacillus as an organism. E. S.

MEDICAL RADIATION BIOLOGY. By FRIEDRICH ELLINGER, M.D., Chief Radiation Biologist and Head, Pharmacology Division, Naval Medical Research Institute, U.S. Naval Hospital, Bethesda, Md. Pp. 945. Springfield, Ill.: Charles C Thomas, 1957. Price, $20.00.

THIS book attempts to fill a sorely needed void: The collection and presentation of the present state of knowledge in radiobiology, and correlation of this information with the basis, indications and restrictions in the medical uses of radiation. Despite the great amount of labor which went into the preparation of this book, and even in view of some important assets of the book, it is the opinion of this reviewer (a radiotherapist) that the book fails to fulfill these needs. The major ground on which it fails is a general lack of critical examination and evaluation of the material presented. This is particularly apparent in the clinical sections, discussing the uses of radiation in therapy, and in the sections on "Effects of Radiation on the Progeny." For example, in the review of the experiences with human fetal irradiation, much of the usefulness of these data is lost by failing to indicate the dose and the time of irradiation after conception.

On the positive side, the bibliography is so extensive and well organized and so readily useful through skimming of the chapters of interest as to compensate for much of the deficiencies of the book. The reviewer believes that the bibliography is of sufficient value to recommend that this book be placed in the library of interested institutions. It is to be hoped that the second edition of the book will improve the defects discussed to the point where it can be generally recommended to all who are interested in informing themselves on this important subject.

R. R.

HEART DISEASE AND PREGNANCY: PHYSIOLOGY AND MANAGEMENT. By C. SIDNEY BURWELL, M.D., Samuel A. Levine Professor of Medicine, Harvard University AND JAMES METCALFE, M.D., Associate in Medicine, Harvard University. Pp. 338; 44 ills. Boston: Little, Brown & Company, 1958. Price, $10.00.

"MOST of sterling worth is what our experience teaches." This book is based primarily upon the authors' experience at the Boston Lying-In Hospital. This experience was obtained from caring for 236 rheumatic, 35 congenital, 2 hypertensive and 4 other cardiac pregnant women. The experience of others carefully documented in the literature is reviewed and compared to their own. This book is a worthy successor to Hamilton and Benton's classic "The Heart in Pregnancy and the Childbearing Age" which also should be required reading for all obstetricians and cardiologists.

In general, the conclusions are conservative. Prophylaxis is advised for all rheumatic pregnant women because pregnancy may mask active rheumatic fever. The authors have not found cardiac surgery necessary for any rheumatic pregnant women nor for almost all instances of congenital heart disease during pregnancy. Special care is needed at delivery for those with abnormal connections between cardiac chamber or great vessels. Interruption of pregnancy may in exceptional instances be necessary for those with acute myocardial infarction, primary pulmonary hypertension and the rare person with disabling congenital heart disease who becomes pregnant.

The style is simple; the text short; the material all meat. This book deserves careful study by all who may at any time be called upon to treat a pregnant woman with heart disease. L. S.

GYNECOLOGIC AND OBSTETRIC PATHOLOGY WITH CLINICAL AND ENDOCRINE RELATIONS. By EMIL NOVAK, A.B., M.D., D.Sc.(HON.), Trinity College, Dublin: Tulane, F.A.C.S., F.R.C.O.G. (HON.), Late Assistant Professor Emeritus of Gynecology, The Johns Hopkins Medical School, Gynecologist, Bon Secours and St. Agnes Hospitals, Baltimore; Fellow and Past President, American Gynecologic Society, and EDMUND R. NOVAK, A.B., M.D., Assistant Professor of Gynecology, The Johns Hopkins Medical School; Gynecologist, Johns Hopkins, Bon Secours, Hospital for the Women of Maryland, and Union Memorial Hospitals, Baltimore, Maryland. 4th ed. Pp. 650; 683 ills., 25 in color. Philadelphia: W. B. Saunders Company, 1958. Price, $14.00.

NOVAK's Gynecologic and Obstetric Pathology has been the outstanding text on the subject since it was first published in 1940. This edition, the fourth, is equally impressive. Emil Novak, the senior author died during the revision, but fortunately his son Edmund, who had worked in the laboratory for several years and was actually working with him on the revision subsequently completed it.

No remarkable changes have been made in the format. The chapter on Breast Pathology has been omitted and one on Exfoliative Cytology has been added. The material on Placental Abnormalities was prepared by Robert E. L. Nesbitt, an authority in the field.

The text, as in the previous editions, includes a considerable amount of valuable clinical information concerning diagnosis and treatment of the lesions discussed. Theoretical considerations of origin, cause and prognosis for the lesions as well as the gross and microscopic patterns are often presented.

The text is profusely illustrated with excellent black and white and colored photographs and photomicrographs of pathologic specimens and with drawings.

This book should be a valuable addition to the library of any physician who deals with gynecologic disorders but it will, of course, be most useful to obstetrician-gynecologists and pathologists. J. W.

The Electrophysiology of the Heart. By HANS H. HECHT AND 43 OTHERS. Ann. New York Acad. Sci., **65**, Art. 6, 1957. Pp. 493; 192 ills. New York: New York Academy of Sciences, 1957. Price, $4.50.

THIS monograph is the outcome of a conference of outstanding scientists of various disciplines sharing a common interest in the electrical manifestations of the heart beat. It serves as a foundation for electrocardiology, based far more on the principles of biophysics and mathematics than on empirical experimentation and experience. The five main parts (each followed by a discussion) deal with 1) Cellular events during the cardiac cycle. 2) Spread of impulse through cardiac muscle. 3) Cardiac recovery. 4) Distribution of electric potentials in volume conductors. 5) Analysis of the surface electrocardiogram.

Science is truly without ending. Scientific and medical specialization has developed to such a degree that it has become difficult for scientists in one area to communicate understandingly with those in even related areas. To help in meeting this problem, conferences such as this are needed. The contributors to this symposium are the outstanding leaders in the field; lack of space does not permit to name all of them: of those from abroad are: Burger, Durrer, and vander Tweel (Netherlands); Schaefer (Germany); Weidman (Switzerland), Sodi-Pallares (Mexico).

Information made available in such a monograph is not available in any texts. The New York Academy of Sciences and the National Heart Institute who sponsored the conference and the publication have rendered a great service.

H. R.

Hormones in Blood. Ciba Foundation Colloquia on Endocrinology. Vol. II. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.CH. AND ELAINE C. P. MILLAR, A.H.-W.C., A.I.R.C. Pp. 416; 74 ills. Boston: Little, Brown & Company, 1957. Price, $9.00.

THIS volume will be of interest to students of the physiology and chemistry of hormones. The series of lectures presented by a group of international experts covers the present advance made in the study of the biological assays of hormones in blood, particularly as regards the pituitary, thyroid, adrenal and pancreas.

W. P.

Second Conference on Sulfonamides. By Perrin H. Long and 31 Others. Ann. New York Acad. Sci., **69**, Art. 3, 1957. Pp. 147; illustrated. New York: New York Academy of Sciences, 1957. Price, $3.00.

Underwriting Canadian Health. View of Welfare Programs. Pp. 165; 2 ills. Toronto: William Lougheed Associates, 1957.

Symposium on Nutrition and Behavior. Edited by Josef Brozek, Professor, School of Public Health, University of Minnesota. Pp. 124; 22 ills. New York: The National Vitamin Foundation, Inc., 1957. Price, $2.50.

The science of human nutrition has encompassed a wide scope of interest, one of the most important aspects of which is the interrelationship between diet, nutritional and biochemical disorders and behavior. In this 14th nutrition symposium held at the University of Minnesota a broad perspective of this problem is unveiled by a group of experts representing a variety of disciplines including sociology, psychology, medicine, public health and psychiatry. Original and specific investigations are presented by the essayists rather than generalities or analyses of the literature. Among the broad subjects considered are: The Impact of Diet on Behavior, Hunger and Appetite, Food Appraisal and Acceptance by Man, and Satiety and Weight Control. Important discussions concerning methodology, clinical assessments and new physiological concepts establish this volume, previously published as an issue of the American Journal of Clinical Nutrition, as essential reading for scientists and clinicians involved even remotely with these subjects. C. S.

A System of Ophthalmic Illustration. By Peter Hansell, M.R.C.S., F.R.P.S., F.B.A.P., University of London. Pp. 114; 78 ills., 5 in color. Springfield, Ill.: Charles C Thomas, 1957. Price, $5.57.

The author's purpose in publishing this monograph is to stimulate the production of good ophthalmic photographs and artistic sketches. Its appeal will be chiefly to those individuals charged with the responsibility of setting up a department of photography and illustration associated with the practice or teaching of opthalmology. The value of a reference of this type can really be appreciated if the physician stops to think of the funds that could be wasted by purchase of the improper equipment and materials. Here is a way to make your entry into a strange field less painful and expensive. L. H.

Occipito-Posterior Positions. By Edward L. King, A.B., M.D., F.A.C.S., F.A.C.O.G., Professor Emeritus of Obstetrics, School of Medicine, Tulane University of Louisiana. Pp. 106; 60 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $3.75.

In this relatively short monograph a complete analysis of the management of occiput posterior positions is presented. Labor and its conduct when occiput is directed posteriorly is discussed and the postural methods presumed to influence anterior rotation are described. Both manual and forceps rotations are considered in detail and the various types of forceps and the methods which can be used to alter the position of the head are presented.

King has long been interested in the management of occiput-posterior positions and has himself described a method for forceps rotation. The book is well written and covers each phase completely yet succinctly. Most of the illustrations have been taken from other publications and they are well chosen and illustrate the material adequately. This book should prove helpful to any physician who is required to perform obstetric operative procedures. J. W.

Is Homosexuality a Menace? By Dr. Arthur Guy Mathews, Former Director and Chief Criminologist for Kings Detective Bureau. Pp. 302. New York: Robert M. McBride Company, 1957. Price, $4.00.

Homosexuality casts a blight on our civilization and poses a threat to the youth of our nation. The homosexual preys on the innocent and the unsuspecting. The mark of chaos in the world today can be attributed to the leadership of sexual degenerate leaders. Homosexuals are spies and undercover agents trained to undermine governments from within.

The author seems to realize that his views regarding homosexuality are not in keeping with the views of many physicians, psychiatrists, sociologists and psychologists. Dr. Mathews claims to have investigated these authors and has discovered that many of them were homosexual and thus expressed biased views.

This book is a diatribe against homosexuality and against anybody who expresses an understanding attitude toward the problem. M.B.

From Sterility to Fertility. By Elliot E. Philipp, M.A., M.B., B. Chir., F.R.C.S., M.R.C.O.G. Pp. 120; 7 ills. New York: Philosophical Library, 1957. Price, $4.75.

Although a number of books and pamphlets on sterility have been prepared for nonmedical readers none covers the material quite so well as "From Sterility to Fertility" by Elliot E. Philipp. He presents first a definition of sterility and a history of its treatment. He then describes the study of each of the partners of an infertile marriage and the causes of failure to conceive. A considerable amount of attention is directed toward emotional factors, artificial insemination and, in a final chapter, adoption.

It is obvious that the author has had a good bit of experience in dealing with infertile couples because he shows a thorough understanding of the clinical problem and the patient's reaction to it. The material is interesting and easy to

read and comprehend. The subject matter is well illustrated by line drawings and by well selected case histories. The latter are used to document certain specific points and none are sensational or objectional.

This small book should prove helpful in assisting an infertile couple to understand the problem and while it cannot replace the physician's discussion with them it certainly should supplement it admirably. J. W.

The British Encyclopaedia of Medical Practice Including Obstetrics, Gynaecology and Other Special Subjects. Edited by THE LORD COHEN OF BIRKENHEAD, M.D., D.Sc., LL.D., F.R.C.P., F.A.C.P., F.F.R., Professor of Medicine, University of Liverpool. Pp. 353. London: Butterworth & Co., Ltd., 1957.

Chronicle of The World Health Organization, Vol. 11, No. 9, September, 1957. Pp. 31; 10 ills. Geneva: World Health Organization, 1957. Price, $.30.

1958 Edition Physician's Federal Income Tax Guide. BY HUGH J. CAMPBELL AND JAMES B. LIBERMAN. Edited by HENRY D. SHEREFF. Pp. 94. Great Neck, N.Y.: Channel Press, 1958. Price, $2.50.

Manuel de Classification et de Détermination des Bactéries Anaérobeis. BY ANDRÉ R. PRÉVOT, Pasteur Institute, 3rd ed. Pp. 362. Paris: Masson et Cie, 1957. Price, 2500 fr.

THIS is one of the well-known paper bound Monographie de l' Institute Pasteur series. Its author rates as the world's authority on the classification of anaerobic bacteria, a subject to which he has devoted much of his scientifically productive career The 2nd edition has been extensively revised and enlarged without, however, any profound change in the author's personal—and unacceptable to many bacteriologists—views regarding arrangement and nomenclature. E. S.

Die Bluteiweisskörper des Menschen (Untersuchungmethoden und deren klinisch-practische Bedeutung). BY PROF. DR. MED. FERDINAND WUHRMANN, Chief of Medicine, Kantonspital Winterthur (Zurich) and DR. ING. CHEM. CHARLIE WUNDERLY, Chief Scientific Assistant in Medicine, University Clinic, Zurich. 3rd ed. Pp. 499; 179 ills. Basel and Stuttgart: Benno Schwabe & Co., 1957 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $13.00.

THE third edition of this book has been almost entirely rewritten to include the authors' summary and interpretations of the tremendous amount of literature on the subject made available since the appearance of the 2nd edition in 1951. Great emphasis has been placed on the technique and interpretation of results of paper electrophoresis and free electrophoresis. There are many beautiful photographs of electrophoretic patterns of serum proteins of patients with a wide variety of illnesses. Th book should be a valuable addition to the library of a hospital clinical laboratory as a source and reference text. It should be worthwhile to physicians who attempt to interpret the results of the laboratory in terms of variations in plasma proteins in the various disease states. R. B.

Clinical Laboratory Methods. BY W. E. BRAY, B.A., M.D., Consulting Laboratory Director, Martha Jefferson Hospital, Charlottesville, Va. 5th ed. Pp. 731; 124 ills. and 18 color plates. St. Louis: C. V. Mosby Co., 1957. Price, $9.75.

ALTHOUGH the latest edition of this well-known volume of clinical laboratory methods is published in a smaller (pocket-book) format than its predecessors, there has been no sacrifice of content. Indeed, the present volume incorporates many new developments in laboratory diagnosis which have been made since the fourth edition appeared some 6 years earlier.

The concise descriptions of methods in this book will be very helpful to those who perform and interpret laboratory diagnostic tests. C. Z.

Versuch der Darstellung des Entwicklungsgeschehens von einem umfassenden Aspekt aus als Arbeitshypothese für vergleichende Forschungen besonders auf dem Gebet der Embryologie. BY DR. MED. GÜNTHER NAUNDORF. 2nd ed., Pp. 36; 3 ills. Hamburg: Günther Naundorf, 1958.

PHYLOGENY is looked upon philosophically. It is believed to be caused by mutation directed by a superior force rather than by adaption to environmental circumstances. W. E.

Hematology for Medical Technologists. BY CHARLES E. SEIVERD, Chief Technologist, Doctor's Clinical Laboratory; Director of Research, The Horizon Laboratories, Glendale, Arizona. 2nd ed. Pp. 275; 158 ills. and 13 color plates. Philadelphia: Lea & Febiger, 1958. Price, $5.75.

THIS is a simplified conception of hematology for medical technologists, in which the various tests are outlined in cook-book style. This book would be of use to those technicians who are taught by an apprentice method, but, unfortunately, it does not adequately provide the hematologic background required by well-trained technologists. C. Z.

Whitla's Dictionary of Medical Treatment. By R. S. Allison, V.R.D., M.D., Queen's University, Belfast, and T. H. Crozier, M.D., M.Sc., Physician, Royal Victoria Hospital, Belfast, and 26 Contributors. 9th ed. Pp. 854. London: Bailliere, Tindall and Cox, 1957 (The Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $10.50.

This type of handy reference work which epitomizes therapeutic knowledge in a single volume has maintained its popularity with many medical practitioners over the years. The first edition of this text, which appeared in 1891, was written by one man, Sir William Whitla. The present, 9th edition, is the work of 28 contributors who have done a very creditable task that will be much appreciated by the generalists in medicine. R. K.

Trends in Gerontology. By Nathan W. Shock, Chief of Gerontology Branch of the National Health Institute and the Baltimore City Hospitals. 2nd ed. Pp. 214; 10 ills. Stanford, California: Stanford University Press, 1957. Price, $4.50.

Since the appearance of the first edition of this work in 1950, the field of gerontology has been growing apace. The author has condensed into this readable little volume the essentials of that progress, a task for which he is eminently qualified by reason of his position as Chief of the Section on Gerontology, National Health Institute and the Baltimore City Hospitals, his compilation and editorship of the most exhaustive bibliography on Gerontology and Geriatrics and his personal observations of gerontologic activities in seven European countries. It is interesting to note the increased emphasis on the role of rehabilitation among the aged in his chapter on "An Institute of Gerontology," which in this country still remains an unfulfilled wish. The book will be helpful and stimulating to all readers, lay as well as professional, who are concerned with the many sided problems of aging and the aged. R. K.

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